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ANNALS OF
INTERNAL MEDICINE

VOLUME VI MARCH, 1933 NUMBER 9

The Senile Patient*

By LEWELLYS F. BARKER, M.D., F.A.C.P., *Baltimore, Maryland*

SOME of you may be wondering how anyone connected with the Johns Hopkins Hospital dare say anything in public about the later life of man in view of the commotion aroused by our great internist, the late Dr. Osler, some years ago through his semi-serious, semi-jocular remarks upon the ages of forty and sixty; but the chairman of our Program Committee, Dr. George W. Crile, whose word is law, has assigned to me as a topic "The Senile Patient", and I must take the risk!

PHYSIOLOGICAL AND PATHOLOGICAL SENILITY

With your permission, I shall interpret the term "senile patient" as meaning simply "a patient advanced in years", avoiding by this definition any necessary connotation of preternatural mental or physical infirmity due directly to old age. For there is, you will grant, an old age that is, relatively speaking, "physiological" as well as a "pathological" old age.

Though a unicellular organism may live on indefinitely, every multicellular organism grows old and ultimately dies. Though its constituent cells may, in cultures in vitro, seem to be potentially immortal, the aggregate of cells of a metazoan animal is definitely mortal. Old age and death are the price paid for the differentiation and specialization of function, characteristic of organisms made up of many cells and tissues that are reciprocally interdependent.

Though there are great differences in the length of life of the individual members of the human species, and though the average duration of human life has been steadily increasing for centuries and more rapidly during recent years (from thirty-five in 1880 to fifty-five in 1920), it is the expectation of life of children at birth and of people in the earlier decades of life that has been most markedly increased; the gain in the expectation of life of persons fifty years old has been only 1.35 in eighty years, whereas the expectation of life for older groups has been growing less, owing to the prolongation of the lives of weaker persons by means of our modern methods of curative and preventive medicine. Many human beings still reach

*Address to the Interstate Postgraduate Assembly, Indianapolis, Ind., Oct. 25, 1932.

the age of ninety or one hundred, but there is, as yet at least, but little if any scientific evidence that the maximal span of human life can be materially increased by any measures that are likely to be devised for the improvement either of man's environment or his heredity. It may not be possible to extend average longevity beyond the age of sixty—almost certainly not if the euthenic practices of the present are not to be supplemented by eugenic practices, to which many are antipathetic.

Biostatistical studies have thrown much light upon the factors that determine the span of life for the human individual. Though longevity depends partly upon inherited constitution, partly upon environment, the evidence strongly favors the view that, on the whole, factors of inheritance are of greater importance than environmental factors. Many years ago, in one fairly large aggregate of persons studied (the Hyde family), it was found that a group that had both fathers and mothers who lived to eighty or more years had an average duration of life of 52.7 years, whereas in the same aggregate, another group in which both parents died before sixty had an average duration of life of only 32.8 years, a difference of practically twenty years. From this and other evidence available the well-known aphorism "To live long, select long-lived parents" would seem to be justified!

In "physiological" old age, there is a gradual process of cell atrophy and a relative increase in the interstitial tissues at the expense of the parenchyma of the organ-systems—an involution of the organism as a whole comparable in process to the involution of single parts of the organism (such as the branchial clefts, the placenta, and the ovaries) occurring at different stages of life. The late Dr. A. S. Warthin spoke of this aging of the whole organism as "the major involution" and of the aging of single parts as "minor involutions"; and he thought that involution was as important as evolution in the great procession of life, minor involutions occurring when parts are no longer of use to the organism, the major involution taking place after the organism as a whole has passed through the periods in which ordinarily the fundamental biological functions have been fulfilled. Theoretically, then, senescence is as physiological as growth; both are inherent in the quality of the germ-plasm inherited. With the best germ-plasms and favorable environments the duration of life of higher organisms is rarely greater than five times the number of years of development to maturity and if the latter for man be taken to be twenty-one, the maximal span of human life cannot much exceed one hundred years, though through preventive medicine and hygiene we may increase average longevity a little more and may swell the numbers of human beings that enjoy a "physiological" old age. But it is better for the race that human individuals live not too long. Thoughtful men must agree with Goethe's statement, "Death is Nature's device for securing abundant life".

The Causes of Death Among the Old

The very old die from causes very different from those that are responsible for the death of younger persons.

By virtue of their inborn qualities of resistance, their good nutritive and reparative powers, the harmonious activity of their several organ-systems, their habits, and their good fortune in the avoidance of lethal exogenous influences (traumata; infections), they have reached advanced years of life, but they ultimately die either from the break-down of some important organ system or from trauma or suicide. The recent statistical studies of Pearl and Raenkham show that with advancing adult age there is a steady decrease of the percentage of total mortality due to diseases of organ-systems normally directly exposed to and in contact with the external environment, whereas there is an increase of the percentage of total mortality due to diseases of organ-systems not exposed to direct contact with the external environment.

Nearly half of our old people die from diseases of the circulatory system (cardiac failure; arterial disease; cerebral hemorrhage); about one-eighth from diseases of the respiratory system (especially lobar and bronchopneumonia); about one-eighth from cancer; about one-twelfth from renal disease; about one-fifteenth from diseases of the digestive system; and the rest from diseases of other organ systems, traumata, or ill-defined diseases reported as "deaths from senility". The last mentioned cause of death should rarely, if ever, be reported; if a definite cause has not been made out, it is wiser to report "death from unknown cause". The majority of deaths among old people occur during the winter months of the year; and more die during the latter half of the night than during the day and the first half of the night. If you have not read the excellent paper by Dr. Alfred Worcester entitled, "The Care of the Dying", let me urge you to do so.

The Somatic and Psychic Infirmities of Later Life

All normal people desire long life, but they usually add the proviso that they shall continue to enjoy both bodily and mental health. As Talleyrand wittily said years ago, "Everybody wants to live long; but nobody wants to be old." Very few people in early life would willingly look forward to a long period of senile decrepitude or chronic invalidism. In his description of the Struldbuggs (who lived forever), Swift painted their plight as so pitiable, when they were observed by Gulliver at Laputa, that any form of death seemed preferable to the continuance of such a life.

The physical infirmities of old age have been much studied through the centuries; since the earlier descriptions of non-medical writers in the Ninetieth Psalm, in Ecclesiastes, and in the literature of the Greeks and the Romans, medical men at all times have been interested in the gradual physical deterioration of the structures and functions of the human body in those who live long. Beginning with failure of accommodation in the eyes, change in the color and abundance of the hair, gradual loss of the teeth, diminution of sex potency, and increased fatiguability, a whole series of other changes are prone sooner or later to become evident, until, if life continue long enough, the fully developed picture of senility is presented. The height is slightly reduced, a stooping posture is assumed, the body-weight decreases,

the bony prominences become more marked, the joints stiff and the muscles flabby, the skin is wrinkled, and shows hyperkeratoses, the arcus senilis appears, the breasts and the abdominal wall become pendent, the thorax grows rigid with shallow respiration and tendency to bronchitis, the arteries thicken, become tortuous, and sometimes calcified, varicose veins and hemorrhoids are common, digestion is slowed with diminution of hydrochloric acid in the gastric secretion and tendency to flatulence and constipation. In men there is difficulty in starting the flow of urine and of complete emptying of the bladder owing to hypertrophy of the prostate, atony of the bladder or both; the genitalia atrophy, the endocrine glands become less active (as shown by the lowered basal metabolic rate, the sensitiveness to cold, the tendency to hyperglycemia and glycosuria, and the changes in libido and potentia), and the sensory functions, motility, and coördination become more or less impaired.

Of the psychic manifestations of later life, some are referable to cognitive, some to affective-conative domains. Among the earlier symptoms are forgetfulness of names, a diminution of the instinctive urges (sex, food, social life), and lack of receptivity of new ideas. Later on, there may be loss of memory for recent events, difficulties of attention, concentration and orientation, somnolence in the daytime and insomnia at night. If the cerebral arteries undergo marked changes, pseudobulbar and other paralyses (with or without aphasias and apraxias) may result, or changes in the psyche (egocentricity, lack of regard for the welfare of others, stubbornness, tendency to suspicion, fall of the ethical level, pathological irritability and emotionalism) may follow. Whether outspoken "senile dementia" (with confusion, illusions, and delusions) and "second childhood" are to be regarded as merely the expression of an intensification and rapid progress of physiological involution of the cerebral cortex, or are to be kept separate from the latter as something more specific, are matters still under discussion. The relations of senile dementia to cerebral atherosclerosis, to Alzheimer's disease, to Pick's disease, and to other organic and functional psychoses of the senium and presenium can scarcely be dealt with in a brief paper such as this, though there is a large and growing bibliography of the subject.

General Comments Upon Diseases in Persons Advanced in Years

Students of geriatrics or presbyatrics (the branch of medicine that deals with diseases of the old) have distinguished between the maladies that are largely restricted to the aged and the diseases that occur in both the young and the old.

Among the former are Paget's deforming osteitis, senile osteoporosis and malum coxae senile, senile anorexia, diverticula of the esophagus and intestine, coproliths, senile bronchial catarrh, senile emphysema, prostatic hypertrophy and its sequelae, cerebral atherosclerosis, senile dementia, paralysis agitans (non-encephalitic in origin), and hyperkeratosis. Carcinoma, too, is much more frequent in the second than in the first half of

life, though in extreme old age its incidence lessens.

Among the diseases that occur in both the young and the old, those of the circulatory and of the respiratory system predominate in the old, but the symptomatology may vary considerably from that observable in the young. In vigorous old people, it is true, the clinical phenomena may not be very different, but in older people in whom characteristic involutional changes have already occurred, we meet with many bizarre, atypical, and more or less confusing clinical pictures.

It has been especially emphasized by internists of experience that *acute infections in the old* exhibit certain peculiarities, including (1) tendency to early collapse because of cardiac failure or failure of the vasomotor or respiratory centers in the medulla, (2) frequency of respiratory complications like pneumonia or capillary bronchitis because of increased rigidity of the thorax, senile emphysema, or stasis in the pulmonary circulation, (3) early cerebral manifestations (delirium, disorientation, coma) because of cerebral atherosclerosis, of lessened resistance of nerve cells to toxins, and of low blood pressure, (4) often evidences of diminished reaction-capacity to infection as seen in low rather than high fever, slight leukocytosis, and prolongation of convalescence, and (5) frequently, absence of any acute splenic enlargement. The local symptoms of infections such as pneumonia and meningitis are often less marked, too, than in earlier life.

Since nearly half of all old people die as a result of some disorder of the circulatory system, the management of *myocardial insufficiency* merits especial consideration in any discussion of the senile patient. The physician attending the old should be ever on the alert for symptoms like dyspnea, edema, and other evidences of circulatory enfeeblement; early recognition is important not only for the prevention of outspoken cardiac decompensation but for the avoidance of uremic intoxication and of cerebral softening so prone to occur in old people whose renal arterioles or cerebral arteries have suffered damage. Many writers warn against giving digitalis preparations to old people, and certainly caution should be observed in using them, particularly when symptoms of heart block, of angina pectoris, of aortic aneurysm, of retinal hemorrhage, of cerebral hemorrhage or embolism, or of severe gastrointestinal disturbances (especially diarrhea) have been present. Nevertheless, I still regard digitalis as a most valuable remedy in old age for the support of the heart muscle after it has begun to fail, especially if caffein sodium benzoate or caffein sodium salicylate be used with it. The particular preparation of digitalis administered is of less importance than the physician's experience in its application. In acute myocardial insufficiency, camphor is, also, a valuable drug. Recently, the combined use of insulin and glucose in the treatment of failing heart in both old and young patients has been coming into vogue. Rest should of course be increased, but, whenever possible, the older patient should be allowed to sit in a chair at intervals, for continuous bed rest has its special dangers for the aged. A few days of Karrell's milk diet, fol-

lowed by a simple cardiac diet of five small meals with restriction of the total fluid intake to 1500 c.c. or less, should be ordered. A daily bowel movement should be arranged for, either by means of mineral oil, psyllium seeds, compound licorice powder, a small dose of saline laxative in the early morning, or, if necessary, by the use of enemata or glycerine suppositories. Gentle general massage daily is advisable but the forms of hydrotherapy and of heart gymnastics resorted to for younger cardiac patients are best avoided in the treatment of the old. Provision should also be made for sound sleep at night by prescribing, where necessary, some barbital derivative, but never chloral preparations; if there be marked nocturnal restlessness, codeine or a small hypodermic of morphine may be given at 9:00 p.m. though caution in the use of morphine in older people is, as everyone knows, important. If diarrhea should develop, it may be necessary, temporarily, to stop digitalis therapy and to administer calcium carbonate, salicylate of bismuth, or tannalbin until the diarrhea is checked. After the signs of circulatory insufficiency have been made to disappear it is well to keep up chronic digitalis therapy for a time. I usually give a half grain of powdered digitalis leaves with 7½ grains of theobromine sodium salicylate thrice daily, after eating, for three weeks out of each month, provided gastrointestinal disturbances do not appear. When edema is marked, we dare not purge or sweat the patient, but rather make use of salt-poor diet and of diuretics like theocin by mouth or like euphyllin by suppository in addition to digitalis, diet, and rest. Many use calomel to promote diuresis, but I prefer to do without it in the treatment of old people. When there is bradycardia with tendency to heart block (Stokes-Adams syndrome), digitalis and strophanthus preparations should be shunned, though atropine is indicated, and caffein and theobromine preparations may be used as vasodilators; in the syncopal attacks, a handkerchief upon which a few drops of amyl nitrite have been sprinkled may be placed over the face for inhalation in the hope of cutting short the attack. Old people who suffer from heart block or from angina pectoris should have with them a small vial of nitroglycerine tablets, placing one on the back of the tongue when needed.

Of the killing diseases of old age, *pneumonia* (lobar or lobular) ranks second to circulatory disease; Dr. Osler used to speak of it as "the old man's friend". Senile lobar pneumonia is often of asthenic type (without initial chill, herpes or pain), with relatively low temperature and without marked leukocytosis. The urine is usually diminished in quantity and in chloride-content. The physical signs are often indefinite and when the existence of pneumonia is suspected, roentgenograms of the chest are most helpful in diagnosis though difficult of application unless the patient happens to be in a hospital when the attack occurs. The mortality is notoriously high. If the patient recovers, the termination is more often by lysis than by crisis. In treating pneumonia in a senile patient, we have to rely chiefly upon general measures, supporting the heart and vasomotor center by cau-

tious administration of digitalis and caffein sodium salicylate, giving inhalations of oxygen, using luke-warm compresses or sponging with alcohol and water (taking great precautions against the chilling of the patient), and paying due attention to skilful nursing, diet, elimination, and provision of fresh air. Immune sera should not, in my opinion, be used intravenously in the treatment of pneumonia in old people.

The Hygiene of Later Life and the Question of Rejuvenescence

Relatively few persons have a "physiological" old age; what has been designated as "normal" or "biological" death at ninety or one hundred (attributed to the wearing out of the energy units of some essential organ, most often in the form of simple senile atrophy of the heart muscle, in the course of the "major involution") is only rarely observed, for most people succumb long before the end of the maximal span for the species, either because of harmful environmental influences, or of inherent pathological defects.

It is the task of our profession to search for both the extrinsic and intrinsic causes of "pathological" old age and to educate the public as to possibilities of preventing it, or of, at least, deferring it. In attempting to solve the problem, we should keep ourselves free from the illusion that we can transcend the limits of the possible. No human organism can live longer than the potential period set by the energy-charge of the fertilized egg-cell from which it starts. The human individual must die, if for no other reason than that this energy-charge must, during life, gradually undergo exhaustion; the human race continues because its germ-plasms receive renewals of energy-charge from generation to generation. In how far the exhaustion of the energy-charge during individual life is related to specific growth stimuli, to specific growth inhibiting factors or to both we do not yet know. Many hypotheses have been advanced with regard to changes in the blood serum and in the physical-chemical equilibrium in the body, to the accumulation of toxic products, and to endocrine disturbances; but, thus far, no hypothesis has found enough support to gain full acceptance.

Medicine has made real progress in the control of the extrinsic factors that prevent "physiological" old age and lead to death before the end of the possible span of life. The average longevity of the human being has been practically doubled since 1800 through the discoveries of curative and preventive medicine and earnest attempts to apply them. Average longevity may, doubtless, be somewhat further increased by an extension of environmental control. We have not yet reached the limits of the possible in the protection of human beings from errors of diet, faulty elimination, insufficient fresh air, physical and mental over-activity and under-activity, and the manifold pathological influences of temperature, light, electricity, mechanical forces, chemical action, infection, and the economic, the psychic, and the social surroundings. This work of protection should be enthusiastically supported with the goal of the theoretically preventable ever in mind. But

we must not forget that it is life expectancy at birth and in the earlier decades that has been increased, whereas expectancy at fifty has been increased very little in the past 100 years and average expectancy for persons of sixty and seventy has, as I have said, been falling.

Progress in the prevention of the intrinsic factors of disease and of premature death due to faulty germ-plasms has been less marked. The world has been slow to recognize and apply the possibilities of a practical eugenics that could, by a breeding-out process, improve the qualities of the germ-plasms from which human beings start. Human nature is, in a way, in conflict with the rest of Nature, and our concern for the human individual is to a certain extent antagonistic to the interests of the human race and of human society as a whole. Our humanitarian impulses compel us to do all that we can to prolong the lives not only of the strong and the "fit" but also of the weaker and the "less fit", so that many of the latter who would otherwise have died early survive to the reproductive period and transmit their faulty germ-plasms to their offspring. It can scarcely be expected that heredo-familial diseases and constitutional defects can be lessened without genetic control. We know a host of these harmful genetic influences now. Any physician who has carefully studied the genealogical records of many families must have been impressed with the significance of both dominant and recessive Mendelian traits for the incidence of disease and for the shortening of life. It is no accident that early arteriosclerosis, cancer, diabetes mellitus, cerebellar ataxia, manic-depressive psychoses, and dementia praecox are especially prevalent in certain families. Even tuberculosis is not wholly a matter of exposure to Koch's bacillus; the constitutional disposition to disease plays a great part in the incidence of and lack of resistance to this and other infections as well as in the occurrence of the more obviously heredo-familial diseases and the mortality due to them. Longevity itself is undoubtedly dependent in part upon exquisitely inheritable components. From what I have said it will be sufficiently obvious that hygienic measures directed toward the increase of the number of old persons that are healthy must, of necessity, give due attention to both genetic and environmental factors.

In the few minutes that remain, may I make brief reference to the special hygiene of later life and also say a word with regard to "rejuvenescence".

Periodic health examinations are valuable for persons over fifty-five or sixty as well as for those who are younger, in order that habits that are faulty for the time of life may be corrected, that any infectious processes present may be brought under control, and that the mind as well as the body may become adjusted to the march of the years. Persons over sixty and especially over sixty-five should sedulously avoid over-exertion, either bodily or mental. More physical rest and fewer hours of mental work may be indicated. Though the body should be regularly exercised, this exercise should be gentle and if any new form be taken up training in it should be grad-

ual. Doubles at tennis are then better than singles and nine holes of golf probably better than tennis. Gardening is a source of joy for many older people. Violent exertion of any kind and undue haste should be forbidden. When the time approaches for the lessening of the strain of occupation, it should be foreseen and the reduction should be made by degrees rather than suddenly. All too often an abrupt retirement from business or professional life has disastrous effects. The rate of progress of the reduction of activities should be individualized, for the rate that is wholesome may vary greatly in different persons. The main thing is "to take in sail" at the right time and gradually. The use of tobacco in reasonable amounts may be permissible, though patients who are developing arterial diseases (hypertension, angina pectoris, or intermittent claudication) may do well to abandon the use of it entirely.

In countries in which the use of alcohol is not prohibited, a little wine or beer or an occasional cocktail, a glass of whisky and water, or a liqueur may be much appreciated by older persons and be beneficial rather than harmful, though any excessive use should be discouraged.

Water-drinking should be regulated; a glass or two a half hour before eating will suffice, whereas an excessive intake of water throws unnecessary strain upon the heart.

A much smaller intake of food than in earlier life is desirable for older persons; after fifty-five, one should each year eat a little less. The meals should be small and should consist of simple, easily digestible foods, the caloric intake being adjusted to the caloric needs. In general, less meat and fats should be eaten than in youth, and foods that cause gaseous indigestion, as well as rich and highly spiced foods of all sorts, should be taboo. Meals should be eaten slowly; the food should be thoroughly masticated but "Fletcherism" is unnecessary. Five small meals are better than three large ones. Breakfast may consist of milk, cereal, a soft boiled egg, coffee or tea, and a little marmalade with toast or a roll; if fish be taken at breakfast, it should be fresh, not salt or smoked. In the mid-forenoon, a glass of milk, an egg, or a cup of soup or a cracker may be eaten. The principal meal should be taken near the middle of the day and may be composed of soup, a small portion of boiled or roast meat, chicken, fish or oysters, two delicate green vegetables, and a little stewed fruit or some cottage cheese and a demitasse of coffee; if the patient be not too heavy, a little mashed or baked potato, or rice, or macaroni may be added. In the afternoon, a cup of tea with a cracker or a little toast may be eaten. The evening meal should be small and devoid of meat; eggs in some form with bread and butter or toast and fresh salad, or (instead of eggs) milk, may be followed by a little stewed fruit or a simple pudding. A small cup of decaffeinized coffee will do no harm.

Older patients should weigh themselves weekly and keep a record of the weight in order that the physician may form a right judgment regarding the optimal caloric intake.

Regular bathing habits should be maintained, but caution should be ob-

served regarding excessively cold or hot water for the bath. Gentle calisthenic exercises in the morning are often advantageous; J. P. Müller's system in which part of the exercises are taken before the bath, and part (with skin rubbing) after the bath, are found helpful by many.

Constipation should be carefully avoided; when it is marked, one must make sure that no enterostenosis is developing. The fruits and green vegetables of the diet recommended together with regular exercise will usually suffice for regular bowel movements, though some persons may require acidophilus milk or a little mineral oil or psyllium seeds in addition. If laxatives are used, they should be mild and should be changed from time to time. An occasional enema may be desirable but I am opposed to the enema habit that so many adopt.

Summer vacations should be spent at the sea or, if preferred, at medium altitudes, where there are forests or shaded walks; very hot and very dry places are best avoided. Winter vacations may be spent in the South or Southwest, especially if there be any tendency to bronchial catarrh.

The dying down of sexual desire and potency in later life seems to be one of Nature's safeguards for older men, especially for those who have had bradycardia, dyspnea, or symptoms of angina pectoris. In any case, great moderation in sexual indulgence is advisable, remembering Wordsworth's saying that "Love in old folk a great dotage is!" Much has been written of late of "rejuvenescence" by means of Steinach's operation or by administration of endocrine products. The evidence favors the view that any rejuvenating effects obtainable are but transitory; there may be a temporary "re-erotization", but this is of doubtful value and not devoid of danger to the older man.

The mental state of older persons should be carefully watched. The physician who undervalues psychotherapy in the management of patients over sixty makes a great mistake. All too many persons, when they first become conscious of the fact that they are growing old become pessimistic, complain that the world is going to the "bow-wows", declare that "life is over" for them, become negligent of personal appearance, tidiness, and social duties, yield to their apathy and diminished interests and become hypochondriacal—attitudes that undoubtedly hasten the aging process. A few go to the other extreme, vehemently deny any change in their physical or mental powers, and, as a sort of overcompensation for the flagging of their powers that they have really felt, tend to become overactive and to outvie even younger people in their lust for pleasures and their enthusiasms. But when the shrewd physician who has observed many older persons detects the premonitory involutional symptoms, he will do all that he can to guide his patients along the right paths, discouraging undue "let-up" on the one hand and excessive epicurean "let-loose" on the other. The older person who is wise will frankly recognize that there are unpleasant features of age that cannot be abrogated; but he will cultivate a philosophy that is based upon the realities of the life of the human individual and of the human species.

He will cling to the fact that every age of life has its own blessings and is good for its own sake, though he will hope that he may be lucky enough to escape from life before "second childhood". As Longcope has recently emphasized, the mere extension of life for "helpless doddering wrecks of humanity" is of but little value; he approves of Stevenson's attitude when he asked the question, "Does not life go down with better grace, foaming in full body over a precipice, than miserably straggling to an end in sandy deltas?" Older persons ought to meet the restrictions that age imposes with courage and common sense and should enjoy to the full the compensations that later life brings—"honor, love, obedience, troops of friends". Like Macbeth, they will determine that "the mind I sway by and the heart I bear shall never sag with doubt nor shake with fear". And as long as possible, they will cultivate their hobbies and continue to participate in the intellectual pleasures of music, art, literature, and science. Thus living, one may, it is true, become old, but he will at least have gone far in the art of bearing age aright.

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The Rôle of Bacteria in Allergy, with Special Reference to Asthma*

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As early as the beginning of the present century the late Victor C. Vaughan[1] already had an adequate understanding of the problems of bacterial sensitization. This eminent biochemist maintained that bacteria, although morphologically simple in structure, are correspondingly complicated in their chemistry and comprise in particular a group of highly complex proteins. His insight into the minute chemistry of bacteria is further evidenced by his account of one or more carbohydrate components which he regarded as intimately linked with the large nucleoprotein molecules. He concluded that these constituents could readily be split apart by dilute acid or alkali, but better by 2 per cent solution of caustic soda in absolute alcohol. The resulting protein nucleus set free was found to be non-specific and poisonous, while the other component, largely carbohydrate, was highly specific but non-toxic.

The further development of this important phase of bacteriology diverges along two general lines. One of these concerns bacterial variation from the smooth, or S-type, into the rough, or R-type, with relative loss of virulence.[2] The other includes the advances in knowledge of the bacterial antigens found in the brilliant and detailed reports of Avery and his colleagues, Zinsser and his colleagues, Lancefield and others, who, working with various pathogenic organisms, have isolated two distinct fractions—a nucleoprotein which is antigenic but not highly specific and a carbohydrate which lacks antigenic power but is definitely specific.

Dochez and Avery[3] in 1917 described a type-specific soluble substance which they had isolated from broth cultures of pneumococcus, and which they decided was a secretory product of the bacterial capsule. Zinsser and Parker[4] in 1923 corroborated Dochez and Avery's result with pneumococcus and reported similar soluble specific substances obtained from cultures of tubercle bacillus, *Staphylococcus aureus*, influenza bacillus, and typhoid bacillus. The same type of specific soluble substance has been isolated from cultures of Friedlander's bacillus,[5] yeasts,[6] *Streptococcus viridans*,[7] hemolytic streptococcus,[8] *Meningococcus*,[9] and members of the coli-typhoid group.[2] These various substances are admittedly of the same nature and apparently resemble that obtained by Pick[10] as early as 1902. It is not necessary to recount in detail the prop-

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erties of these soluble bacterial products. Full descriptions are to be found in the reports of Avery and Zinsser and their co-workers.

Mention should be made of other soluble antigens and corresponding antibodies recently attributed to the pneumococcus. Sabin[11] found that Type I antipneumococcus serum, after the total precipitation of the anticarbohydrate precipitins, retained a definite amount of its type-specific protective action which was not neutralized by additional SSS ("specific soluble substance"). It could be absorbed, but only by the homologous virulent pneumococci. Enders[12] reported in the autolytic products of pneumococcus Type I a substance distinct from SSS but reacting specifically with its homologous antiserum. In weakly alkaline solution this is destroyed by boiling but not in acid solution. It resists peptic digestion and appears to belong, like SSS, to the group of haptenes. Such findings suggest the possibility that bacteria contain in their infinitesimal makeup an indefinite variety of specific protein compounds which are capable of acting as antigens and of inciting the formation of antibodies in the animal host.

It may not be out of place here to attempt a tabulation of various bacterial effects which have been described.

1. Foreign non-specific protein action has been reported by Miller[13] and others, and may be regarded as having some importance. Coca and his collaborators,[14] in their comprehensive text on allergy, conclude on inadequate premises that the idea has been "relinquished that vaccine treatment is a specific form of therapy". In this presentation I shall admit the existence of such a procedure as protein shock therapy but at the same time draw a distinction between this type of treatment and the highly specific vaccine therapy employed by the Dicks and Dochez in scarlatina and by various workers in bacterial asthma. Topley and Wilson[15] presented at length the experimental evidence against the reputed importance of the non-specific factors. They concluded that there is no evidence that any non-specific stimulus can cause the appearance of any of the known serum antibodies. While there is some evidence that such non-specific stimuli may cause an increase in any of the normal antibodies or a secondary rise in titre when administered after the effect of the preliminary specific immunization has reached its zenith or begun to decline, the responses falling within this category are irregular or trivial and never comparable to those following the reinjection of the specific antigen. Pilot[16] and others, working with the skin reactions in man with staphylococci, found that of fifty-six patients suffering from staphylococcus infection 89 per cent reacted positively and often more violently than normal persons. From this it might be inferred that mere infection is identical with sensitization. On the other hand, Pottenger,[17] referring to infection with another organism, calls attention to the important conception that a relatively greater hypersensitivity of the cells is likely to be present in the earlier and more active stages of the infection than later. Others[18] have reported anaphylactic and even asthma-like symptoms in guinea pigs from repeated intravenous and intratracheal

injections of green-producing streptococci. The results, while not very striking, were said to resemble in many respects the corresponding human respiratory phenomena.

2. The Vaughan and Friedberger[19] split products must be considered as possible toxic factors in any infectious disease but accentuated in their importance in hypersensitive states.

3. Production of histamine-like substances with resulting bronchospasm by bacteria of the *B. Friedlander* group has been reported by Knott and Oriel and is described in the Report of Research at the Asthma Clinic of Guy's Hospital for 1928-1930. Harkavy[20] had found a spasm-producing substance in the sputum during asthmatic attacks which was absent during the free interval. These findings are of interest in comparison with the observation of Koessler, Hanke and Sheppard[21] that histamine could be produced in the intestinal tract by various members of the coli-typhoid group.

4. The nucleoprotein and SSS fractions of Avery and others have already been mentioned and the research of Sabin and of Enders suggests the probability of a multiplicity of specific soluble products of bacteria.

5. The Arthus[22] phenomenon is a special type of accelerated allergic response in rabbits and other animals. After several daily inoculations of a foreign protein without noteworthy effect, subsequent inoculations of the same type produce a hard aseptic infiltration which persists for days or even weeks.

6. The Shwartzman[23] phenomenon is an unexplained skin response to bacterial filtrates and is elicited as follows: The sterile filtrate of the broth culture is injected into the skin of rabbits and after twenty-four hours a suitable amount of the same filtrate is injected intravenously. This results within four or five hours in a hemorrhagic necrotic swelling of the originally injected skin sites. This phenomenon has been produced with cultures of several different bacteria even if filtrates from entirely unrelated bacteria were used for the skin-preparatory and injury-producing factors respectively. The skin-preparatory substance is, however, of a specific antigenic nature and neutralization of either the skin-preparatory or injury-producing factors is possible only through the use of homologous sera.

7. The Dick[24] toxin differs from the SSS of Avery in that, although heat resistant, it gives rise to a specific antiserum.

8. The observations of Touart[25] and others that old quiescent vaccine inoculation sites are relighted by subsequent inoculations of the same vaccine in a different location deserve comment. Patients have repeatedly called my attention to this phenomenon.

These various manifestations of bacterial action have been listed to call attention to the multiplicity of antigens and effects coming from bacterial metabolism and the corresponding complexity of reactions on the part of the host. It is entirely conceivable that some of these specific and nonspecific bacterial agencies enact an appreciable part in the pathogenesis of infectious asthma and other hypersensitive clinical states attributable to bacteria.

Sensitization to Bacteria

It is a matter of common observation that certain cases of asthma, rhinitis, migraine, urticaria and other allergic conditions are unexplainable on the basis of reaction to the ordinary foods and inhalants. It is equally evident that the causes of most of these must be sought in the infectious processes within the body. In general, the workers in this specialty of medicine have divided their cases into bacterial and non-bacterial, or categories which are equivalent. The only matter of disagreement concerns the question of specificity or non-specificity in the bacterial causes.

There can be no reasonable doubt that bacterial infection may, by its mere presence in the bronchial tree, cause irritation of the vagus nerve endings or bronchial musculature directly and thus furnish the modus operandi of the bronchospasm and attendant exudation and edema of asthma. In accordance with this many authorities maintain that vaccine treatment in asthma is nothing more than foreign protein shock therapy. This same line of reasoning applies also to the protein split product theories of Vaughan and of Friedlander, or to the bacterial histamine-like bodies of the Guy's Hospital Staff. It is entirely possible that any one or more of these non-specific chemical factors may be operative in certain instances. The pioneer research of Vaughan has indicated that any bacteria, including the relatively avirulent *B. coli* group, have an inherent toxicity for the animal organism.

We are, however, equally concerned with the more specific effect of the pathogenic microörganisms on the human subject. I refer to those manifestations of bacterial action which are characterized by definite sensitization phenomena.

Several difficulties present themselves at once. The first of these is the supposed discrepancy between human allergy and animal anaphylaxis, owing to the frequent failure to obtain passive sensitization of animals by injections of allergic sera. I am inclined to agree in this regard with Zinsser[20] that we should not neglect the basic principles of hypersensitiveness in favor of discrepancies which represent gaps in our experimental knowledge rather than fundamental differences of principle. Another and more formidable obstacle lies in the extreme complexity of the bacterial antigens and antibodies as compared with those of the simpler coagulable proteins.

Bacterial anaphylaxis has been thoroughly established as a scientific fact. "Active and passive sensitization may be induced with bacterial antigens, as determined by the occurrence of anaphylactic shock (Rosenau and Anderson 1907, Kraus and Doerr 1908, Holobut 1909, Kraus and Admiridzibi 1910, Zinsser and Parker 1917, Tomcsik and Kurotchkin 1928), or by Dale's technic with the isolated uterus (Zinsser and Parker 1917, Zinsser and Mallory 1924, Tomcsik and Kurotchkin 1928). The reactions are specific and desensitization can be demonstrated.

"Sensitization to bacterial antigens cannot, however, be produced with the same ease and certainty, as in the case of horse serum or egg-white. A single injection of bacteria, or bacterial extract, frequently fails to produce any

demonstrable sensitization, and the most successful results have been obtained by those workers who have employed repeated small injections of antigen for sensitization, followed by an interval of three weeks or so".[15]

Zinsser[26] has cited convincing instances of laboratory sensitization with tuberculin. The evidences of bacterial anaphylaxis are, however, relatively slight in degree. Zinsser and Tamiya[27] attribute this limited formation of antiprotein antibodies, and consequently of true anaphylaxis, to the fact that coagulable protein, though present to a slight extent in bacterial extracts, does not predominate in the bodies of the bacteria. The bacterial hypersensitiveness which concerns us in asthma and other allergic conditions is essentially different from the anaphylactic phenomenon. Its development is usually dependent upon the presence of the whole bacteria in the organism and appears to be related to the nucleoprotein-carbohydrate combination of Avery, Zinsser and others. The complex chemistry of the bacterial cell body contains other substances which may well assume importance in sensitization phenomena when their properties have been more thoroughly studied.

Clinical Observations

Classification of Allergic Cases. In the absence of a better classification I have grouped my asthma cases according to their causes, into (a) non-bacterial, (b) bacterial, and (c) mixed bacterial and non-bacterial. Group (c) represents the experience gained from extensive testing with foods and dusts. Reactions to these, even though numerous and definite, imply merely a sensitiveness of the skin to the individual allergen and do not in any sense preclude a coexisting bacterial sensitization which may be the underlying process. Many striking instances of this class might be cited.

The routine procedure in my practice is to test the dermal reactions to the foods and dusts with which the patient comes in contact. Regardless of reactions or their absence the possibility of bacterial causes is investigated. A careful history of previous outbreaks of infection, especially in their relation to asthmatic attacks and to seasonal variation, is of help. Certain laboratory procedures, such as the leukocytic and eosinophilic counts, the sedimentation velocity of the blood, the character of the sputum and the results of proper culturing, when combined with physical inspection and the diagnostic employment of iodides and other medication, usually give a fairly accurate determination of the type of asthma.

The choice of material for culture is as important as the technic. Sputum, and in particular Curschmann spirals, are washed in sterile saline, ground in a mortar with sterile sand and cultured with addition of the patient's blood or serum in pour plates and brain broth, also at times streaked on agar and Sabouraud's medium. The blood agar pour plates made on a decimal scale of dilution enable a count of the various bacteria of the sputum. These include in order of frequency *Streptococcus viridans,* hemolytic streptococcus, non-hemolytic streptococcus, *Staphylococcus aureus,* pneumococcus, and others of less importance. The

number of organisms in 1.0 c.c. of sputum ranges from a few thousand to many millions.

We are probably concerned equally in asthma with the intestinal flora. As stated by Zinsser[26] sensitization of the lung does not necessarily imply that the hypersensitive state is relatively more marked in the lung tissues. In my experience culture of the feces carried out according to a rigid technic[28] which inhibits the growth of the intestinal gram-negative organisms has yielded definite results in asthma and other allergic conditions. By this method the normal individual and the non-bacterial sensitization case usually give a negative or negligible culture, while the subject with bacterial allergy will, in the majority of instances, give a growth of pathogenic intestinal bacteria ranging from 100,000 up to many millions from each loopful of stool plated out. In one case it was estimated that one loopful of stool contained 127,000,000 green-producing streptococci. The organisms encountered are, in order of frequency, *Streptococcus viridans, hemolyticus, non-hemolyticus, Staphylococcus aureus* and rarely other organisms.

Many of these asthmatics showing a preponderance of pathogenic cocci in the feces have complained of colitis with loose movements and sometimes with blood and mucus in the stools, especially at the time of asthmatic seizures. Probably a still greater percentage have suffered with constipation. A minority, even in the presence of extreme infestation of the bowel by pathogens, complain of no irregularity in the matter of movements. The presence of a high grade infestation, with or without noticeable clinical disturbance, is to be regarded as a potential cause of asthmatic paroxysms.

In addition to the almost routine culturing of the sputum and feces, cultures are made in selected cases from the sinuses, tonsils, teeth, and other foci. A variety of organisms is obtained.

In other allergic conditions than asthma, including bacterial rhinitis, eczema, dermatitis, urticaria, migraine, and certain rheumatic and ocular conditions, culturing has often been carried out according to methods suited to the condition. Particularly illustrative of the broad application of the principles of bacterial sensitization here enunciated are several cases of iritis referred to me for study. Two out of four such cases treated with streptococcus stool vaccines have shown diverticulosis of the colon on X-ray of the abdomen. Strangely enough, these two with diverticulosis have apparently recovered under vaccine treatment, while the others are still refractory. This subject will be presented in detail in a separate report. Infection in relation to eczema will also be reported separately.

Preparation of Vaccines. In an effort to obtain vaccines which should contain the specific principles of the causative organisms, the following types of bacterial preparation have been studied: (a) washed organisms killed at 60°C. for one hour; (b) unheated Berkefeld filtrates from brain broth cultures containing patient's serum; (c) whole broth cultures in brain broth containing patient's serum and including both the bacteria and their medium.

Each of these types of bacterial preparation has been used in a considerable series of cases for testing and treatment. All have been found specific and have been used with success in treatment. Their relative merits will be discussed following a short summary of the cutaneous reactions. In addition to these three preparations the protein fraction of thoroughly ground bacteria has, in certain instances, been obtained by precipitation with cold alcohol and tested cutaneously on patients. (Figure 1, D).

The requisites for success in vaccine treatment have been proper choice of foci for culturing, careful isolation of the predominant organisms as determined by plate counts, and standardization of dosage by cutaneous tests and systemic reaction. It is also important to employ a type of bacterial preparation which shall include the specific causes of asthma.

Cutaneous Reactions. The reactions obtained in a series of 500 cases of asthma, including a smaller series of 232 cases studied in greater detail, lead me to agree with Thomas,[29] Famulener and Touart, Haibe[30] in Belgium and others that the reactions of intradermal tests in conjunction with the systemic effects of bacterial inoculation form the most reliable

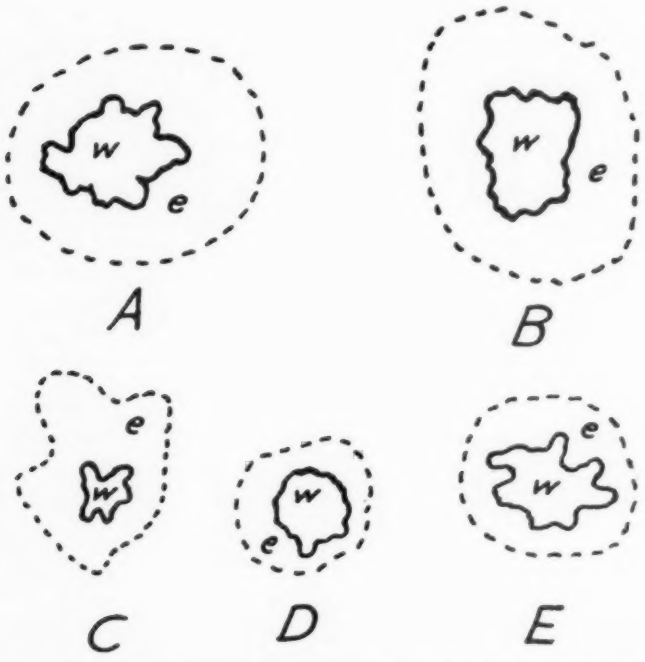

FIG. 1. Tracings of intradermal reactions to bacteria (natural size). *w.* wheal; *e.* erythema. *A.* immediate reaction to *Streptococcus viridans* stool vaccine in patient with canker sores. *B.* immediate reaction to *Streptococcus viridans* stool vaccine in asthmatic patient. *C.* twenty-four hour reaction to hemolytic streptococcus showing small wheal together with erythema. *D.* early reaction to purified protein from *Streptococcus viridans* of stool of asthmatic. *E.* vaccine reaction of same organisms as *D.* (The bacterial reactions are larger than the protein reactions.)

guide to vaccine therapy. It seems advisable to test the reactivity of the skin to the separate bacterial preparations — washed bacteria, filtrate, and whole culture — and to study the use in treatment of those which react.

In evaluating the reactions, most authors are of the opinion that the immediate wheal and its surrounding erythema are of non-specific origin due to the foreign material in the medium and the purely toxic effect of the bacterial extracts. In general my results support this contention. Having repeatedly tested patients with bacterial products and with the homologous sterile medium incubated under similar conditions, I can state that in the great majority of instances the medium produces an immediate intradermal reaction entirely comparable to that with the corresponding whole vaccine. In such cases the reaction must be regarded as non-specific.

Attention must, however, be called to occasional exceptions to this rule of which I shall cite only a few. Figure 1, B is from a tracing of the immediate wheal and erythema from intradermal inoculation of a *Streptococcus viridans* stool vaccine in an asthmatic four years of age. Control inoculations in normal individuals were small and lacking in pseudopodia. The twenty-four hour reaction was entirely negative, yet within ten hours following the inoculation the patient developed a severe attack of asthma. This fact, together with the favorable outcome of vaccine treatment, leads me to believe that this child's immediate reaction was of a specific nature and that it constituted the essential skin manifestation of his bacterial sensitization. Figure 1, A represents a tracing of the immediate reaction to a *Streptococcus viridans* stool vaccine inoculation in a boy who had had canker sores in the mouth for years. Despite the absence of a twenty-four hour reaction this boy made a prompt recovery from his mouth condition and gained progressively in weight and strength. Other such instances might be cited indicating that the immediate reaction is occasionally of primary importance. To these might be added a few other cases in which a significant immediate wheal is followed by a definite delayed intradermal reaction.

As a rule, however, the characteristic cutaneous response to intradermal inoculations is represented by changes in the inoculation site occurring in ten, fifteen, or twenty-four hours, rarely later. Because of the variability in the length of this period it is advisable to make repeated inspections during the first twenty-four hours. I have even had cases of multiple inoculations in the same patient in whom certain reactions showed best at fifteen hours and later faded, whereas others were scarcely visible until twenty-four hours had elapsed.

The character of the cutaneous response is variable. The most usual type resembles that commonly seen in the Dick test and I have accordingly followed the practice of doing the latter test on the same arm as a control, particularly in connection with those cases infected with hemolytic streptococcus. At times the Dick test gives a result which agrees with that of the autogenous hemolytic streptococcus filtrate and vaccine; on other occasions

the two are at variance. A finding which is sometimes overlooked in both is the occasional appearance in fifteen or twenty hours after inoculation of a wheal followed several hours later by a reddish areola of the same size, or even much larger. (Figure 1, C). At times a deep reddish papule forms the center of the areola, especially in *Staphylococcus aureus* reactions (figure 2), and this may even have a yellowish purulent-looking but sterile apex (figure 3).

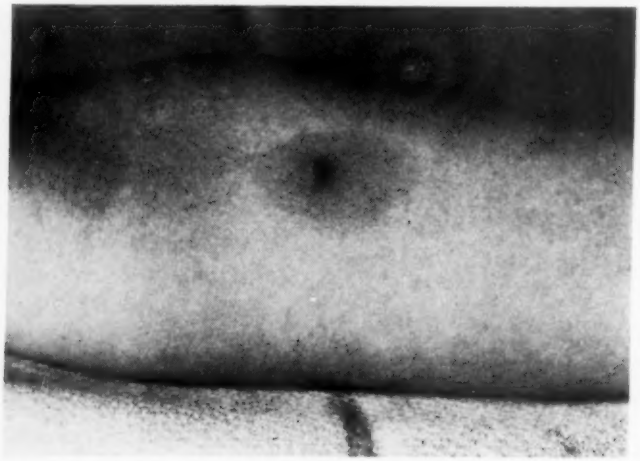

FIG. 2. Twenty-four hour reaction to intradermal inoculation of 0.02 c.c. *Staphylococcus aureus* nose vaccine of asthmatic. Note papule in center of areola.

Reactions of *Streptococcus hemolyticus,* when present, are usually entirely comparable with the ordinary twenty-four hour response to the Dick test. Of interest in this connection is the observation that, in the definitely positive hemolytic streptococcus cases, the response to the Dick test may be equally great (figure 4), or may be lacking (figure 5). It seems probable that the hemolytic streptococci encountered in the sputum and feces of allergic cases may be immunologically homologous with those found in scarlatina* or may be entirely dissimilar.

The site inoculated with washed hemolytic streptococci may react more strongly than the point inoculated with unheated filtrate from the same culture, or the reverse may occur. More often both respond about equally (figure 6).

Streptococcus viridans and *non-hemolyticus* recovered from the respiratory or intestinal tract of asthmatics usually elicit cutaneous responses which are similar to those obtained with *Streptococcus hemolyticus.* In the case of the former groups the washed organisms, or the whole brain broth culture, usually react more strongly than the unheated filtrate (figure 7), although the reverse is occasionally true.

*In one child five years of age, apparently belonging to this group, I treated a violent asthmatic upset by intravenous injection of 20.0 c.c. of antiscarlatinal serum with such a prompt and gratifying result that I feel I should recommend the procedure for consideration.

Staphylococcus aureus, since it grows better in solid media, has been used in the form of emulsions of washed and heated organisms. The behavior of these following intradermal inoculation is similar to that of the streptococci except for the more frequent production by the former of reactions having a papular or pseudopustular center. Other organisms are occasionally employed in my vaccine therapy but have not received the same detailed study as the foregoing.

The vaccines employed usually include both heat-killed bacteria and unheated filtrate. This practice is based on the assumption that the filtrate and bacterial capsule probably contain a predominating amount of the specific SSS haptene of Avery while the bacterial bodies retain the bulk of the less specific, but antigenic, nucleoprotein fraction. The choice of the particular cultures which enter into the vaccine is, however, made on the basis of cutaneous reactions and, to some extent, of the relative preponderance of each organism in the original focus.

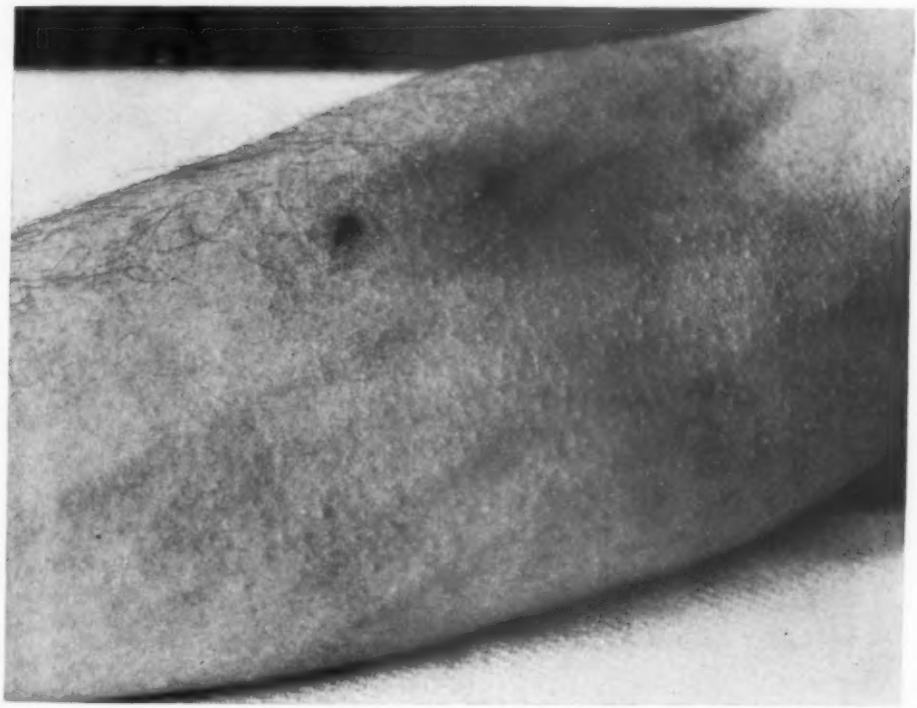

FIG. 3. Twenty-four hour reaction to intradermal inoculation of *Staphylococcus aureus* nose vaccine of dermatitis case, containing in the midst of the areola a papule with yellow center.

Having mixed together those cultures which are considered of probable importance, a trial dosage is worked out on the basis of the sensitiveness manifested by the skin and on general reactions if such occur. The usual

dilution is 1:20 or 1:50 in terms of whole broth culture, or, if several strains are included, dilutions of 1:100 or occasionally even 1:1000. By starting with a minute dosage, say 0.05 c.c., it is generally possible eventually to desensitize the individual to the bacterial antigens. When this is accomplished the dosage, and even the concentration, are increased in the hope that the individual may "pass through an allergic state into one of immunity to the same agent".[26]

FIG. 4. Twenty-four hour reactions to intradermal inoculations of vaccines and filtrates in asthmatic patient. 1. hemolytic streptococcus sputum vaccine; 2. hemolytic streptococcus sputum filtrate; 3. *Streptococcus viridans* stool vaccine; 4. *Streptococcus viridans* stool filtrate; 5. Dick toxin.

Results of Vaccine Treatment. The results of treatment along the lines mentioned have been entirely favorable. Any tabulation of figures in this regard is subject to a great range of error owing to personal factors in the patient such as lack of coöperation and veracity, geographical considerations, overwork, and others. The figures have, however, been collected for what they may be worth and include those 232 cases of asthma in my practice which have been worked out in sufficient detail to permit analysis. Of these, 21 were non-bacterial and were treated on the basis of elimination or of specific inoculations against the offending foods and dusts; 94 were classed as of bacterial origin and subjected to vaccine therapy; and 117 were considered of mixed bacterial and other origin and given vaccine treatment along with suitable attention to

FIG. 5. Twenty-four hour reactions to intradermal inoculations of vaccines and filtrates in asthmatic patient. *D.* Dick toxin, negative. *Sp.* sputum vaccine, mild reaction. *Sp. F.* sputum filtrate, negative. *St.* hemolytic streptococcus stool vaccine, moderate reaction. *St. F.* hemolytic streptococcus stool filtrate, moderate reaction.

the non-bacterial allergens. The results are best expressed in a simple tabulation.

The results in the bacterial group are almost identical with those in the other groups. In past years I have shared the prevailing American opinion that definite reactions to foods and dusts offered the only real outlook for successful asthma treatment. This feeling has undergone a reversal accompanied by a corresponding improvement in results. The English insistence on metabolic and other systemic factors has wrought considerable change in our conception of asthma. The greatest single stride, however, has been a growing appreciation of the rôle of bacteria in asthma, and considerable credit for this phase of the develop-

TABLE I

	Non-bacterial	Bacterial	Mixed	Total
Cases	21	94	117	232
Complete or nearly complete relief	24%	22%	24%	23%
Moderate relief	29%	29%	38%	34%
Slight relief	19%	28%	23%	25%
No relief	5%	10.5%	3%	6%
Result unknown	23%	10.5%	12%	12%

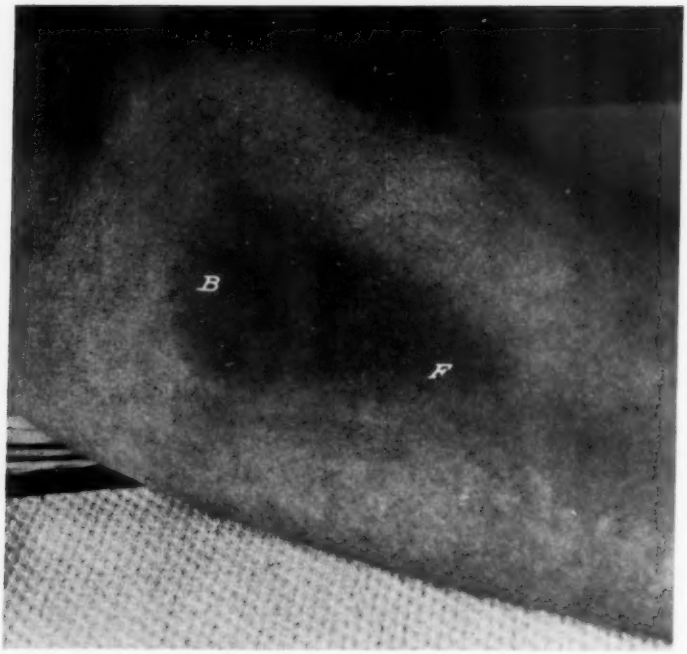

FIG. 6. Twenty-four hour reactions to intradermal inoculations of hemolytic streptococcus stool vaccine and filtrate of asthmatic patient. *B*. vaccine reaction; *F*. filtrate reaction.

FIG. 7. Twenty-four hour intradermal reaction to *Streptococcus viridans* sputum vaccine and filtrate in same patient as in figure 6. *C*. vaccine reaction; *F*. filtrate reaction, very slight.

ment belongs to Sir Almroth Wright[31] and Fleming in England and to Walker[32] and Thomas[29] and his coworkers in America. I am forced to agree with Haibe[30] of Belgium that too much stress has been laid on the cutaneous reactions to foods and dusts in the American reports. He considers that many of these are false reactions and that in any case they may not furnish the key to the allergy.

Of more value than any table of figures is a detailed analysis of individual cases of bacterial sensitization with records showing relative bacterial desensitization through specific treatment. I could cite many instances in which a minute intradermal inoculation of autogenous bacterial antigen has, within one to several hours, precipitated a violent paroxysm of asthma, notwithstanding the fact that a control inoculation of fully 100 times the quantity of stock vaccine has failed to produce a similar effect. Equally convincing evidence for specificity is afforded by the prompt and complete cessation of asthmatic attacks which not infrequently follows the initial intradermal bacterial inoculation of the proper size. The following is a typical example. The patient, a girl of eleven years, had had asthma continuously without any complete intermission from the age of two. At the time of her first visit she was a pitiful spectacle, in an advanced stage of emaciation, and with chest deformity of the pigeon type. Cutaneous tests proved her sensitive to grass pollens, horse epidermal extract, housedust, and many foods. Stool culture yielded hemolytic streptococcus in large numbers, and culture from the nares gave *Staphylococcus aureus*. Repeated inoculations with minute doses of the undiluted vaccines were followed by an increase of the asthma, and the patient returned home in a worse condition than when she came to me. Several months later she returned for observation. Her first week in Portland was devoted to laboratory procedures, and no relief of her asthma accompanied the change of climate. At that time an inoculation of 0.05 c.c. of a 1:10 dilution of the original vaccine was given her and resulted in a complete cessation of her asthma for the first time in nine years. There was no return of symptoms during the following week, at the end of which she left for home. This case is cited as an example of the aggravation of symptoms which frequently follows overdosage of vaccine and the prompt relief which can result from a proper dosage. Many cases might be cited which are equally convincing and in which the relief of symptoms has lasted over a period varying from one to several years.

Either type of specific systemic reaction, that with provoked paroxysm or that with prompt cessation of attacks, constitutes a favorable prognostic sign, especially when supplemented by definite cutaneous reactions. In either type subsequent repeated inoculations on an ascending scale of dosage has usually resulted in improvement. It has thus been found possible to decrease or remove the hypersensitiveness to the bacterial causes and sometimes, though not always, to produce an eventual immunity. Two typical cases will be cited in this connection.

The first patient, a female past middle age, had had severe asthma dating

from an attack of lobar pneumonia in 1913. Sputum vaccine containing streptococcus and pneumococcus gave relief in this early phase of her infectious asthma. In 1917, following a recurrence of asthma, she had a cholecystectomy at the Mayo Clinic with good recovery. Her asthma, however, recurred intermittently until 1925. At this time she consulted Dr. A. Fleming at St. Mary's Hospital in London. This worker cultured the stool, found large numbers of streptococci of the viridans type and started vaccine treatment with small doses of this growth. Perfect relief occurred in three weeks and lasted without incident over a period of five years. In 1930 she suffered another mild attack which responded promptly to a similar stool vaccine made by me. This case affords a striking example of the outstanding infectious nature of this group of asthmas.

Another case, a boy of ten, had had asthma every winter from the time of his measles, diphtheria, and pneumonia six years before. Cutaneous tests resulted negatively with the exception of dog, mustard, and flaxseed, all of which gave good reactions. No specific treatment was given for any of these reactors. A high incidence of eosinophiles in the blood and sputum, together with an increased sedimentation velocity, and the hibernal nature of his attacks led to a diagnosis of bacterial asthma. The sputum, which was scanty and of a whitish milky appearance, yielded on culture over 12,000,000 green-producing streptococci per 0.05 c.c. Stool culture gave 1,600,000 green-producing streptococci and 55,000 hemolytic streptococci to the loopful. Both vaccines gave good twenty-four hour reactions on intradermal inoculation and significant immediate reactions were also obtained with the stool vaccine (figure 1, E) and with the protein prepared from the ground up green-producing streptococci. (Figure 1, D). This boy's asthma stopped within a few weeks after vaccine treatment and has not recurred during the whole winter season. In the meantime his weight has increased from 60 to 73¼ pounds during the past six months. Such cases as this represent bacterial asthma with complete desensitization following minute doses of the specific inciting cause.

Discussion

An analysis of the results of specific bacterial therapy is made difficult by the complexity of the bacterial effects in the human organism. These include not only the over-emphasized foreign protein factor but the more significant specific nucleoprotein-carbohydrate antigens which have been established on a scientific basis by the brilliant researches of Avery and Heidelberger,[33] Zinsser, Lancefield and many others. Sabin and Enders have contributed to our knowledge of these specific phenomena and the Dicks and Dochez have added an entirely different hemolytic streptococcus factor, a true toxin which is heat resistant but which incites a specific antitoxin. Any of these components may be present in the bacterial filtrate or capsule or cell body in varying degree, and it is conceivable that any or all of them may be concerned with the manifestations of asthma.

Some attempt has been made to de-

termine the relative importance of the bacterial cell bodies and filtrates. Intradermal tests with these separate bacterial preparations have shown at times a stronger reaction with the one or the other but just as often the two have reacted equally. There have been instances in which the washed organisms have produced a large twenty-four hour areola while the filtrate has scarcely reacted at all. The reverse has sometimes occurred. Such considerations have led me to a routine procedure of using in treatment those bacterial preparations from the sputum or stool or other sources which reacted best, including in most cases both whole organisms and unheated filtrate.

The results have been studied analytically but detailed tabulations have been omitted, because they were considered highly involved and to some extent misleading. The results do, however, lead to certain important generalizations. Table 1 shows that the outcome of treatment in the bacterial and mixed groups has compared favorably with that in the non-bacterial group, due to known foods or dusts. The success obtained is attributed to the selection of cases on the basis of symptomatic and seasonal considerations, routine blood and sputum examination, and exhaustive culturing followed by administration, in carefully standardized dosage, of those bacterial preparations which have given significant cutaneous reactions. Cases conforming to these requirements and receiving an adequate course of specific treatment have generally had a successful outcome while the others have more often failed of a good result.

The importance of thorough attention to the various food and dust factors has been referred to in a previous report and need not be dwelt on here, nor have the metabolic, endocrine, and other general considerations been overlooked. Space has permitted only the detailed handling of the subject undertaken, namely, the rôle of bacteria.

Conclusion

The limited value of non-specific protein shock therapy is admitted. More important, however, in properly selected bacterial cases is the definitely specific desensitization which can be attained by the careful use of autogenous vaccines and filtrates.

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A Method of Evaluation of Results in Hay Fever; Its Application to Certain Modes of Treatment*†

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THERAPEUTIC progress in any field necessitates a means at our disposal for measuring therapeutic results. This may imply either an objective method or a good subjective method. In hay fever this is especially desirable because of the natural variations in the symptoms. From time to time various treatments are advocated in hay fever and it becomes necessary to measure their value. Modifications in technic of old accepted forms of treatment must also be evaluated. In addition, the measurement of therapeutic results in hay fever may be of worth also in the study of other factors such as age, complications, climate, etc.

Unfortunately there is no objective method for studying results in hay fever. We must rely entirely on a study of the subjective symptoms. The usual means of studying and reporting hay fever results are very unsatisfactory. The most common method, perhaps, consists of grading results according to the physician's impression of the symptoms for the entire season. Frequently the patient himself is asked to evaluate the season after it is over. It hardly needs comment to contend that such a method has too many elements of unreliability. Our powers of recollection become diminished in proportion to the time that has elapsed, and this is especially true if the memory is an unpleasant one.

Even the impression gained day by day from studying the immediate or daily effect of treatment is not of great value unless certain factors are taken into consideration. As long ago as the middle of the nineteenth century Blackley[1] noted that there were marked variations in the pollen content of the air during the hay fever season. He also noted that the severity of the symptoms in himself, as well as in other hay fever sufferers, depended chiefly on the concentration of the pollen in the air. This concentration he measured by counting the number of pollens on a unit area of an oiled glass slide exposed to the atmosphere for a unit of time. Duke and Durham[2] in 1928 emphasized this dependence of severity of symptoms on pollen concentration. They say: "The marked irregularity of the charts (pollen) often accounts for variation in the symptoms displayed by patients from day to day during a given season".

For many years practically all men in the field of allergy have held or ex-

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pressed similar views. It remained, however, for Rackemann and Smith,[3,4] Acquarone and Gay,[5] and Hopkins[6] to show graphically this correlation of symptoms and pollen concentration. The symptom curve of Rackemann and Smith is drawn from results of 100 treated patients. The symptoms for each patient are shown by a horizontal line, a light one for mild symptoms and a heavy one for severe symptoms. The symptom curve is obtained by counting the individual lines where they cross the upright date lines, allowing two counts for the heavy lines, and plotting the totals to make the symptom curve. The objection to these curves is that the symptoms are not graded sufficiently, thus not making sufficient distinction between symptoms of varying severity from day to day. No attempt is made to show how treatment of one type or another may influence this symptom curve.

In 1931 Acquarone and Gay[5] reported a study of the correlation of hay fever incidence in sixty-seven treated patients with that of pollen incidence during 1929. In this study the cases were divided into four groups: tree cases, grass cases, plantain cases, and ragweed cases. The percentage of cases in each group showing symptoms on each day was plotted with the curves made from the pollen counts. On the whole their figures show correlation between pollen counts and the percentage of patients showing symptoms. However, in the ragweed cases, judging from their chart, the correlation was not very constant. The objection to their data and figures is that no discrimination is made between slight sneezing and severe hay fever; "a patient who had symptoms for as short a period as one hour is included in the curve".

Two months after the previous publication, Gay[7] made a more extensive report of hay fever symptoms in relation to treatment. The patients kept their own records, marking the day "bad" if the symptoms persisted continuously throughout the twenty-four hours; "poor" if there were an hour or two of symptoms during the twenty-four hours; and "good" if there were no symptoms at all. He thus finds, for example, in 1929 that the treated cases averaged a total of 14.4 days of discomfort (8.4 mild symptoms and 6.0 days severe), as compared with a possible 46.2 days in untreated patients. In the ragweed group of that year the treated cases experienced 14.1 days of symptoms, against a possible forty-two days in untreated patients.

Hopkins[6] also reported a study of the correlation of the pollen with the symptom curve, but she also did not differentiate between grades of severity.

Method

The first step is the grading of symptoms. The patient who goes through the season with a little sniffling and no discomfort has an entirely different result from one who has severe symptoms with frequent discomfort. It seemed to me, therefore, in order to arrive at any valuable conclusion as to treatment, etc., there must be a grading of symptoms intermediary between a few sneezes and the most severe form of hay fever. The following plan was adopted and carried out during the 1929 ragweed season. The

symptoms were graded into five classes. Grade 1, "very slight", consisted of only an occasional sneeze; this degree of irritation and sneezing would be ignored by many patients unless their attention was aroused by close inquiry. Grade 2, "mild", consisted of definite hay fever symptoms lasting an hour or two of the twenty-four hours. Grade 3, "moderate", was defined as including the more continuous symptoms, lasting a great part of the twenty-four hours, but not of a very violent nature and without much blocking of the nose. Grade 4, "severe", consisted of blocking of the nose, frequently repeated severe sneezing spasms, very marked rhinitis, or marked eye and throat symptoms; any or all of the above symptoms were present but not constant throughout the twenty-four hours. Grade 5, "very severe", consisted of the same symptoms as Grade 4, except that they were practically constant throughout the twenty-four hours.

From such daily grading, individual symptom curves may be plotted as seen in chart 4. It may readily be seen that not only is there a tendency for these curves to be correlated with the pollen curve, but each individual curve gives us a graphic idea of the severity of the season for that particular patient.

Chart 1 represents a composite symptom curve obtained by charting and averaging the daily symptoms of a series of patients. Each patient's daily symptoms are represented by a dot. The dots for that day are then averaged, thus giving us an average

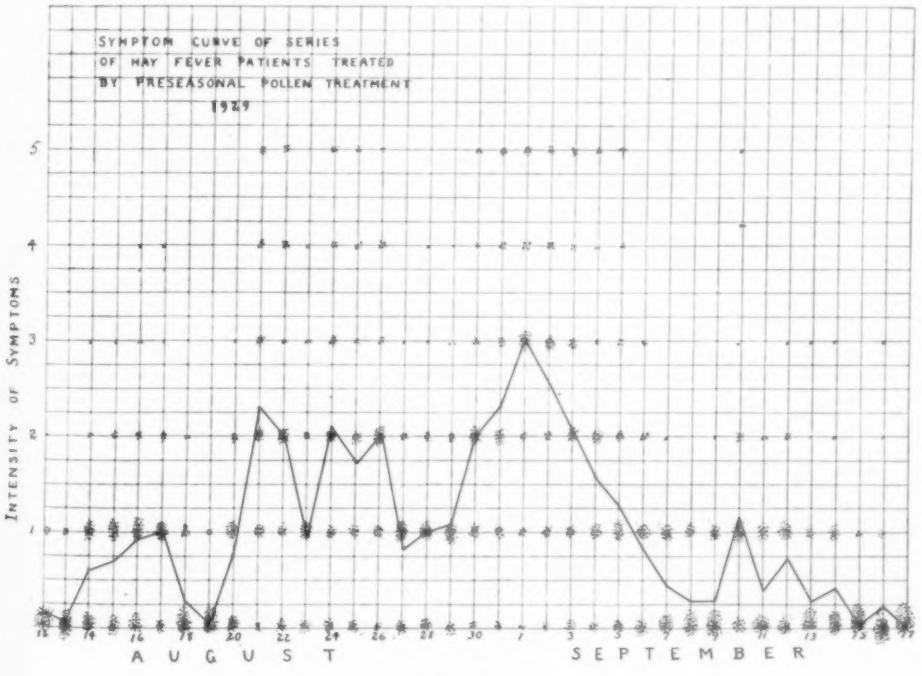

CHART I

daily symptom grade. When all these daily points are connected there is obtained a curve such as outlined in chart 1. The chart is made from a series of fifty ragweed hay fever patients.

Chart 2 shows the correlation of this composite symptom intensity curve with the pollen concentration curve. It will be noted that the severity of symptoms follows pretty closely the changes in pollen density. It will also be noticed that in some places on the graph sudden drops in pollen concentration are followed by more gradual changes in the symptom curve. This is probably due to the tendency for persistence of pathological changes in the nose even after the pollen has ceased to be present in the air. On the other hand, I fail to find any decided lag between the peaks of the pollen curve and those in the curve of hay fever intensity. Acquarone and Gay[5] found such a lag of twenty-four to seventy-two hours, possibly because they were charting hay fever incidence rather than intensity of symptoms. At this point it may be observed that on chart 2 it is also apparent that the average maximum intensity of hay fever symptoms in the treated cases, occurring at the height of the pollen season, is Grade 3, or "moderate", and that during most of the season the average intensity was below Grade 2, or "mild" hay fever.

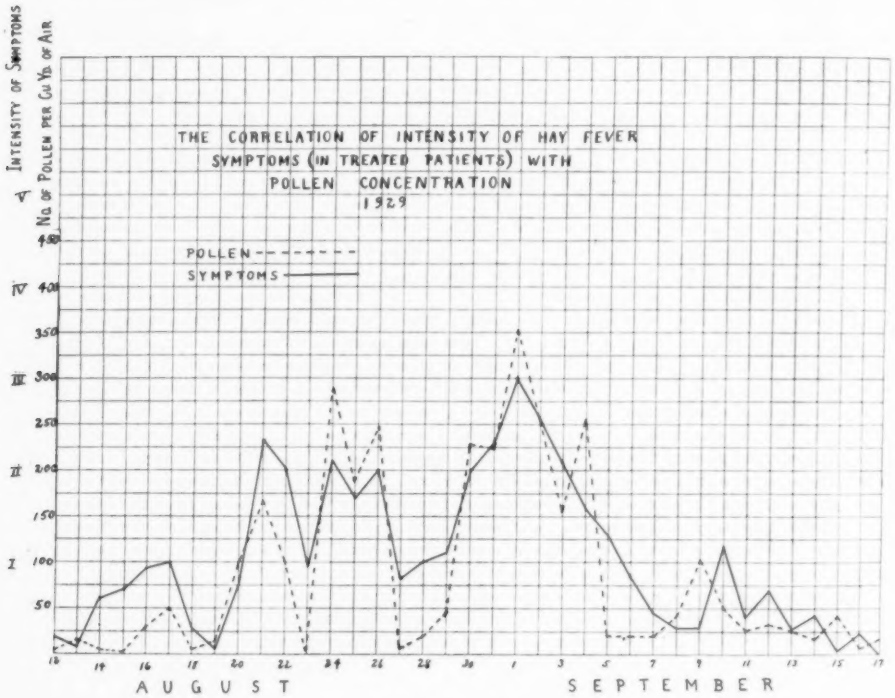

CHART II

In chart 3 we have a comparison between the symptom curve of the previously described treated series and the curve of a series of thirty patients

who were untreated or only partially treated. It is evident that in the latter curve there is also a correlation between the intensity of symptoms and the pollen concentration. It is also apparent that the suffering of the average patient among these untreated cases reaches a greater intensity and is near the maximum for a large part of the season. The "untreated" patients in this series comprise chiefly those who came in at the beginning of the season and had only partial pollen treatment, and those who came in the middle of the season and had only palliative treatment. It is practically impossible to have a series of hay fever patients under observation during an entire season without any treatment whatsoever—the sufferers are not quite content to be thus neglected. It is therefore not unreasonable to think that the symptom curve of a series of absolutely untreated patients would be at a greater height than is depicted in chart 3.

Thus far it may be seen that in any group of hay fever patients the results may be ascertained from a consideration of the average symptom curve or from a consideration of the individual symptom curves. Chart 4 contains five such individual symptom curves, each of which illustrates the usual result under the conditions noted in the chart. It must be emphasized that these individual curves are only examples of their particular series, and that there is considerable variation within the series. However, they serve the

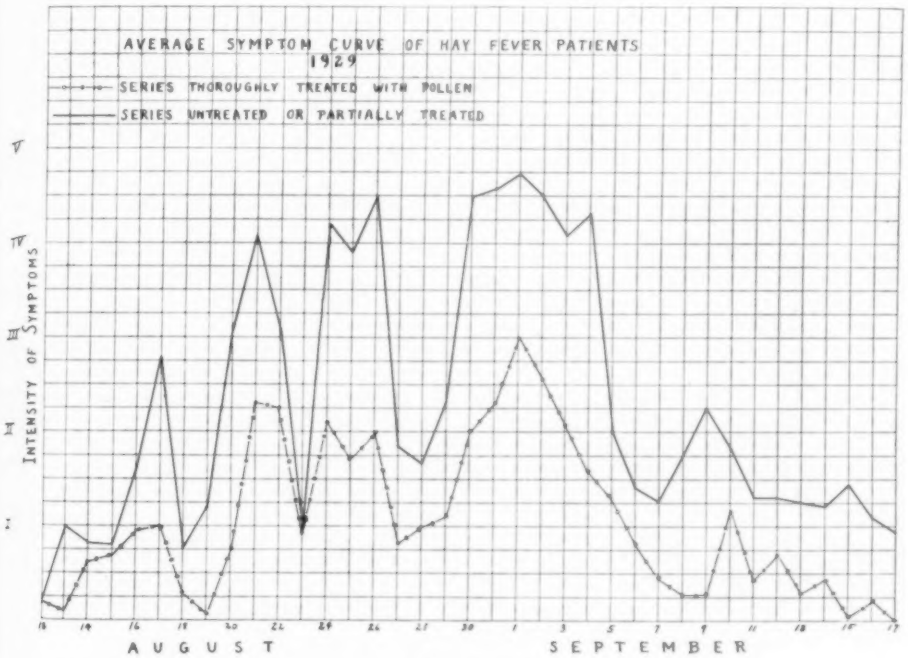

CHART III

purpose of illustrating the types of curves usually obtained and their interpretation.

The bottom heavy curve shows the typical course of symptoms in a case in which treatment was fairly successful. It will be seen that this patient had many days with no hay fever whatsoever, only one day of "severe" symptoms, and the remainder varying from "slight" to "moderate". The curve also shows the variation in the symptoms dependent on the pollen concentration. The curve immediately above it depicts the symptoms of a patient who has had insufficient treatment. The correlation of intensity of symptoms with the pollen curve is again evident, but the curve is at a higher level.

The upper three curves represent patients who had considerable hay fever and on whom various methods of treatment were tried during the course of the season. It will be noted in each case that the medication had no effect on the course of the disease. The symptoms continued to be severe and varied with the pollen density in about the same way as might have been expected without treatment. In the top curve it may be seen that the use of "salvamin" begun on August 26th apparently resulted in marked improvement in the patient's symptoms for the next two or three days; but when one consults the pollen curve it is obvious that the fall in the latter was responsible for this improvement. The continued use of this drug did

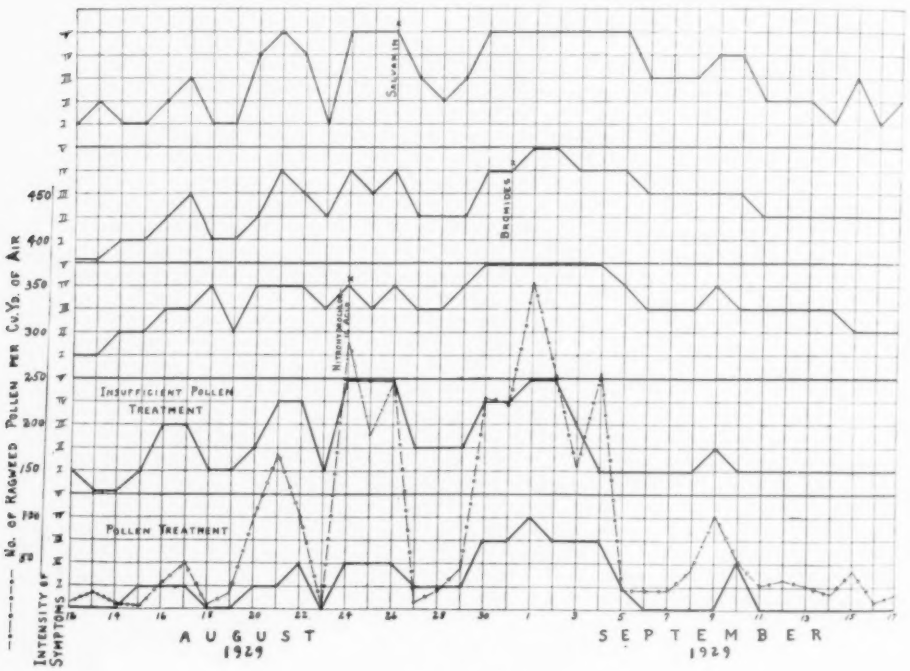

Chart IV

not prevent a recurrence of severe hay fever when the pollen count rose again.

For comparing results, it is seen that not only must the individual twenty-four hour periods be graded, but the results of the entire season must be evaluated also. The problem here is a little more difficult and there probably can be no absolute measure since the usual suffering of all hay fever patients is not the same and what would be a satisfactory result in an extremely severe case might be a decidedly poor result in another. Of course, it is possible to work out a complicated system for measuring degrees of such results, but it probably would add confusion. I have chosen the following designations: failure, poor season, fair season, good, and excellent. An "excellent" season may be defined as one in which the patient has had no hay fever or very slight symptoms. A "good" season is one in which there has been some hay fever but not enough most of the time to be annoying. A "fair" season is one in which there was definite improvement but in which nevertheless hay fever was present during much of the time. A "poor" season is one in which it can be ascertained that there was some improvement, but not enough actually to relieve the patient from his suffering. It is only slightly removed from a "failure", which latter term speaks for itself.

Thus, after evaluating the results in individual patients and then tabulating the results in a series, we can apply the data made available to finally determine the value of a mode of treatment in hay fever. For example, in a series of sixty-two cases of ragweed hay fever during the same season treated by adequate pollen therapy 40.5 per cent had "excellent" results, 30.5 per cent "good", 13.2 per cent "fair", 8.9 per cent "poor", and 6.9 per cent "failures".

On the other hand, the nitrohydrochloric acid treatment, which has been so enthusiastically advocated by some,[8] when evaluated by such a procedure as that discussed above, is shown to be unsatisfactory. For example, in a series of thirty cases during 1929 and 1930 only one had excellent results and possibly two more had fair results. Bromides,[9] also lauded by some in hay fever, gave no results in a small series of cases. For several years "salvamin", which is the lactone of gallic acidethanolaminochlorhydrate, has been enthusiastically advocated in Germany.[10] A series of eight of our local ragweed cases treated with this drug, when tested out for results by the above discussed methods, showed no effects whatever from the use of this remedy.

In the 1931 ragweed season in a small series of nine hay fever patients the effect of intranasal applications of "cold quartz" radiation (ultraviolet) was tried at the request of the Council of Physical Therapy of the American Medical Association. The previously described method of evaluating results was employed in these cases. Except for slight temporary improvement in a few, lasting one or two hours, this therapeutic procedure failed to produce results.

Summary

1. There is need for a method of evaluating the results in hay fever therapy.

2. Any such method must take into

consideration the natural variability in symptoms due to daily, seasonal, and local variation in pollen concentration. Daily pollen counts are absolutely essential.

3. The method of evaluating the results of any hay fever therapy consists of the following steps:

(a) The grading of the individual patient's daily symptoms,

(b) The grading of the patient's entire season,

(c) The tabulation of the results of the entire group under investigation,

(d) The comparison of the total results in such a group as compared with groups treated by usually accepted methods and with untreated cases.

4. The above mentioned method was applied to such proposed remedies as nitrohydrochloric acid, bromides, "salvamin", and intranasal quartz light therapy and showed these to be of no practical usefulness.

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The Patch Test in the Diagnosis of Contact Dermatitis*

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THE greatest problem in the conquest of eczema is the determination of the etiology in a given case. Attempts have been made to differentiate between those cases of eczema due to internal causes and those due to external irritants, the former being designated as eczema and the latter as dermatitis or dermatitis venenata. Such a distinction is often impossible on clinical grounds and should be made only in the presence of positive substantiating proof. The possible exception is a clean-cut case of dermatitis due to poison oak or poison ivy. Here the presence of the eruption in irregular blotches and streaks where branches and leaves have rubbed against the exposed parts of the body is suggestive. Also the usual violent type of vesiculation and edema, especially if coupled with a history of exposure within twenty-four to forty-eight hours prior to the onset of the eruption, is usually sufficient to establish a diagnosis.

Fundamentally there is no difference either histologically or in most cases clinically between an eczema of internal or external origin. The essential point is not a matter of labelling a given eruption eczema or dermatitis venenata but of proving the etiology and of incorporating it in the diagnosis. No one could quarrel with a diagnosis of eczema (food allergy) or eczema (primrose), although if one preferred to use the designation dermatitis venenata (primrose) the diagnosis would be equally valid.

Sometimes the location of an eczematous eruption will suggest an external etiology, but too much dependence should not be placed on such evidence as it will often prove misleading. For instance, arsenical dermatitis due to intravenous therapy or to poisoning from contaminated food, may first manifest itself on the exposed parts of the body and may for a long time show a predilection for these areas. In such cases exposure to the sun aggravates the eruption, but it would be telling only half of the truth to say that such a case of eczema was due to idiosyncrasy to the sun's rays, and if the investigation went no further the patient certainly would not be cured.

Such misleading clues are frequently encountered. It becomes all the more important, therefore, to prove the relationship between a given eczematous

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eruption and a suspected irritant. The so-called scratch test, in which a small amount of an antigen, usually food, pollen, or hair protein, is mixed with tenth normal sodium hydroxide and applied to the skin by means of a small scarification on the arm, is useful, especially in cases of food sensitization and in some instances of eczema due to contact with animal hair or pollen. Instances have been encountered, however, in which a scratch test with a pollen was negative while the patch test was strongly positive.

The patch test, therefore, is particularly useful in detecting those substances, protein and non-protein, which by external contact produce an eczematous reaction. The test has been used for some years in Europe, but it is only during the past three or four years that it has been employed to any extent in this country.

The first essential is a detailed history with especial reference to contact with possible irritants in the patient's occupation, hobbies, surroundings, the local use of medication or cosmetics, etc. There are two important points in such a history which may be confusing. The fact that a patient has handled a certain substance for many years without irritation is no proof that this substance may not be the cause of the present eruption. The skin resistance to a given substance may break down or, to put it in another way, the skin may become hypersensitive after prolonged contact, so that an attack of eczema ensues after each subsequent exposure. The second confusing point is the fact that the eruption may be caused by contact with a given irritant at one point, for example on the arm, and may spread over large areas of the body. It is also important to remember that any substance, no matter how benign it may appear, may be the cause of the eruption in question.

When a careful history has narrowed down the list of probabilities, the test is applied in the following manner. Every effort should be made to simulate the original condition under which the irritation took place. If the substance is a chemical it should be applied in approximately the same dilution to which the patient has been previously exposed. Leaves of plants and shrubs should be as fresh as possible. Dry powders may be moistened slightly with water. The substance to be tested is placed on a small square of cotton about the size of a postage stamp which is then applied to the flexor surface of the forearm, or other suitable area, and covered with a square of some impervious material such as cellophane, which should be about four times as large as the test area. This external covering is then held firmly in place by wide strips of adhesive tape. The space on all sides between the edges of the central cotton square and the edges of the cellophane is sufficient to prevent the adhesive tape from coming too close to the test area. Otherwise the mild temporary irritation which usually results from the adhesive tape might interfere with an accurate interpretation of the reaction. The patch test is allowed to remain undisturbed for twenty-four hours unless discomfort from irritation justifies its removal before this time. A positive reaction is characterized by a sharply defined square of

redness corresponding in size and shape to the central test area. Papules and vesicles are also usually present, corresponding to the appearance of the original eruption. Evidences of the reaction can usually be noted for three or four days or longer after the test is applied. In rare instances the reaction may not develop for forty-eight hours after the test is applied.

The test is simple, inexpensive, and closely simulates the natural conditions under which the dermatitis developed. It is usually very accurate. A few cases have been reported in which only certain areas of the skin were hypersensitive so that in the case of a dermatitis of the face, a patch test on the arm was negative while one performed on the face after the eruption had subsided was strongly positive. Such instances are probably uncommon, but the possibility should be borne in mind.

Clinical Review

During the past two years, we have made patch tests on forty-seven private patients; of these twenty-four have been positive, twenty-one negative, and two of doubtful interpretation. The value of the test lies not only in the positive reactions which definitely establish the etiology, but also in the negative results which exclude certain suspected substances. In nine of the twenty-one patients who did not react to the patch test, subsequent investigations along other lines revealed other causative agents such as fungi, yeast, arsenic poisoning, food and pollen allergy, and infection with demodex folliculorum.

The following is a list of the substances which have given a strongly positive reaction in the twenty-four cases in this series.

Plants:

Primrose, lantana, geum, wigandia, summer grass, wild mustard.

Cosmetics:

"Dew" (for hyperidrosis), henna, (red and bronze), Inecto (hair dye). These positive tests were all obtained on the same patient.

Drugs:

Ammoniated mercury ointment (two per cent), butesin picrate ointment (three cases), adhesive tape (B & B), procaine (two cases), oil of eucalyptus, ephedrine sulfate solution, ephedrine butesin (Abbott 1755).

Industrial Irritants, Etc.

"Calcium", a liquid containing essentially 40 per cent calcium chloride, used in hardening cement.

Union cleaning solvent.

Gas gauge fluid (a red liquid used in the gasoline gauge on the dashboard of certain automobiles).

Ground rubber and cement.

Many other substances have been reported which have caused eczematous eruptions by local contact, and doubtless many others hitherto unreported will in the future be incriminated by means of patch tests. Cases of poison oak dermatitis are usually so characteristic that we have made no effort to control such a diagnosis by the patch test.

A few of the cases in this series are sufficiently interesting to justify reporting them briefly in order to illustrate certain points. The danger of placing too much reliance on circumstantial evidence and on the clinical appearance is well demonstrated in the cases of two dentists who were seen within a few days of each other, both of whom presented eczematous eruptions on the hands.

CASE I

Dr. D.S.B. had had an eruption of the hands and fingers at intervals for one and a half years. He had used procaine for two and a half years before the onset of the eruption. For a period of eleven months since the onset of the eruption he had remained away from his office and during this time the hands had remained well. The eruption had reappeared four or five days after his resumed use of procaine. A second vacation of six weeks resulted in a disappearance of the eruption which, however, recurred within a few days after his return to work. A detailed general history did not reveal any abnormalities. The eruption involved the fingers and consisted of a scaling condition which extended beneath several of the nails. (Figure 1) The right index finger presented a few deep-seated vesicles. Microscopic examination of scales and vesicles was negative for fungi. "Mosaic" forms were found on microscopic examination of a few insignificant scales from between the toes. A patch test of procaine solution was still strongly positive four days (figure 2)

FIG. 1. Procaine dermatitis in a dentist. (Case I)

after it was applied and had not entirely disappeared four weeks later. The reaction was slow in developing, not reaching its height for at least forty-eight hours after the test was applied. Eight months later the patient injected two minims of procaine into his arm. An area of redness developed within twenty-four hours; the anesthesia lasted for three and a half days following which the entire area sloughed out. When the same amount was injected into the arm of his associate, the anesthesia lasted only three and a half hours and there were no evidences of irritation.

CASE II

Three days after Dr. B. had made his last visit, Dr. L.W., also a dentist, consulted us about an eruption of two weeks' duration on the hands. There were areas of redness and scaling with a tendency to fissuring on the fingers and backs of the hands and an especially irritated area on the left

FIG. 2. Positive patch test with procaine. (Case I)

index finger. (Figure 3) There was some scaling between several toes. A patch test with procaine was negative after twenty-four hours and showed no sign of reaction during the next five days. Microscopic examination of scales from the hands, macerated in 40 per cent potassium hydroxide, showed typical chains of spores. "Mosaic" forms were found in scales from the feet. A culture from the toes was positive for monilia. No culture was made from the hand.

FIG. 3. Epidermophytosis involving index finger and thumb. Negative patch test with procaine (patient was a dentist). Positive microscopic examination for spores. (Case II)

These two cases afford an interesting problem in differential diagnosis. The clinical appearance in both cases was similar and the exposure to procaine was suggestive of a contact dermatitis. The positive patch test and the negative microscopic findings in the one case, and the negative patch test and positive microscopic findings in the other established a clean-cut diagnosis in both.

Many instances of hypersensitiveness to butesin picrate have been reported in the dermatological literature and three such cases occurred in this small series of twenty-four patients. One of these cases illustrates not only the type of the eruption but also the spreading of the rash to areas apparently not originally in contact with the irritant.

CASE III

J.M., a boy about twelve years old, injured his left elbow which was immobilized with adhesive strapping. A few weeks later a blister developed under the adhesive. The adhesive was removed and butesin picrate ointment applied. Considerable irritation resulted and several other remedies were tried, but were not successful in controlling the eruption. When he reported for observation the eruption had been present for about one month and had involved extensive areas of the body. The left arm was red, edematous, oozing, and crusted. The face, neck, chest,

FIG. 4. **Dermatitis venenata due to butesin picrate.** Note marked inflammatory reaction at site of application (left arm) and also involvement of face, neck, and anterior chest, e.g., areas not having had contact with the original irritant. A positive patch test was obtained. (Case III)

and other arm presented a more diffuse erythematous, blotchy appearance. (Figure 4) This diffuse eruption had been present only a week. Under the use of mildly astringent and antiseptic wet dressings the eruption gradually subsided. Patch tests were made with butesin picrate ointment and with adhesive tape. The adhesive tape did not irritate but the test with butesin picrate was strongly positive.

CASE IV

Mr. H.C. represents another instance of irritation from butesin picrate ointment, showing also a delayed reaction from the test. Two weeks before coming in, he was badly sunburned while driving in an open car with the top down. Two days later he applied butesin picrate ointment which seemed to irritate. The "sunburn" seemed to last an unusually long time but was gradual-

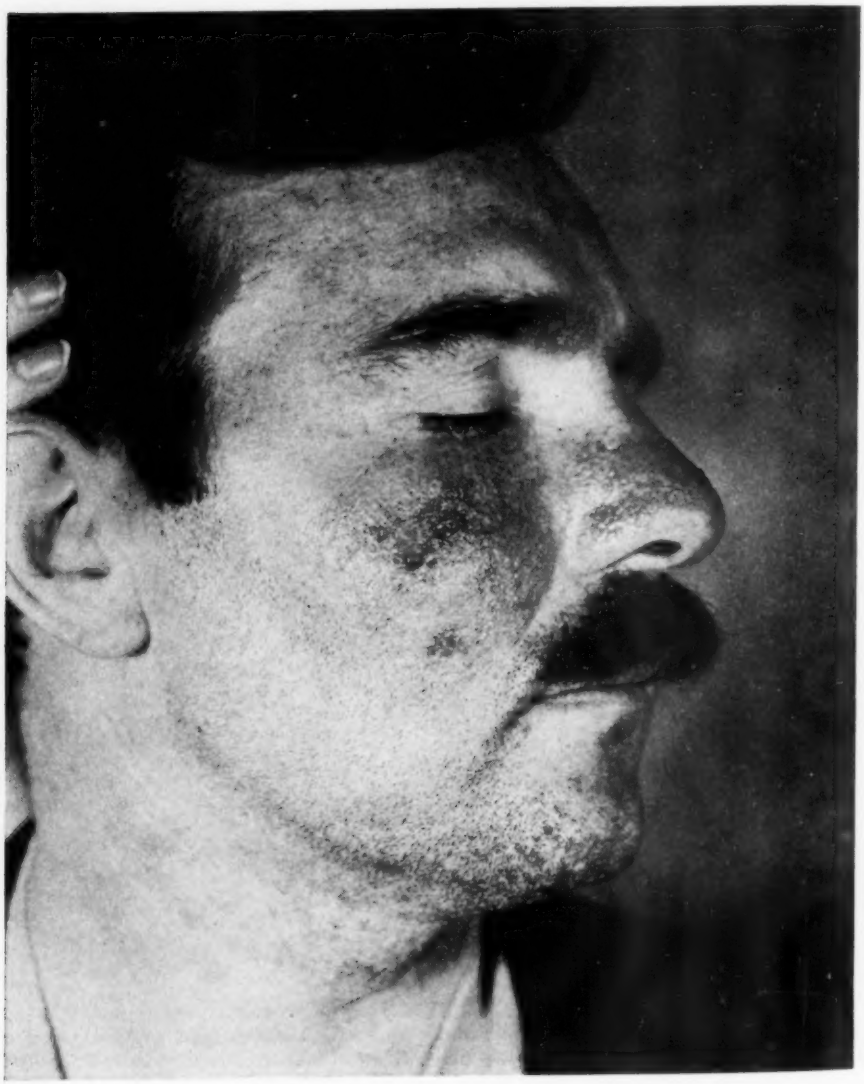

FIG. 5. Dermatitis venenata due to butesin picrate ointment. (Case IV)

ly subsiding, when the night before coming in he again applied butesin picrate ointment. This resulted in a severe flaring-up of the eruption. Examination revealed an eruption limited to the face and neck, and especially pronounced on the front of the cheeks and nose, which were diffusely red, covered with vesicles, yellow crusts, and serous exudation. (Figure 5) A patch test with butesin picrate ointment was negative on removal twenty-four hours later but began to develop redness and vesiculation within a few more hours. Two days after it had been removed the test area was still violently inflamed.

Butesin picrate contains two substances, both of which have been known to cause irritation. Picric acid is a tri-nitro-phenol and butesin is butyl-para-amino-benzoate.

Henna, a vegetable dye, is usually regarded as an innocuous coloring preparation for the hair. In fact some textbooks state definitely that it is non-irritating. Inecto, a proprietary dye, also claims to be free from irritating properties. That such dogmatic statements are unjustifiable is shown by the following case.

Case V

Mrs. J.M., a beauty shop operator, had been having an eruption of the hands and arms at intervals for two months. The present eruption had been in evidence two days. The eruption was limited to the hands and arms, extending for a short distance above the cubital spaces. The entire involved areas were red, edematous, covered with exudate and crusts and fissured in places. The greatest involvement was on the flexor surfaces. (Figure 6) There was a mild erythemato-vesicular eruption on the face and chin. Patch tests were made with eleven preparations used in hair-dressing. Inecto, red henna, and bronze henna gave strongly positive reactions after twenty-four hours, the greatest reaction being caused by red henna. Five days after the eruption had subsided, a new outbreak began on the fingers, spreading to the hands, forearms and several days later to the anterior aspects of the thighs just above the knees where she had rested her arms. This recurrence followed shampooing a woman's hair which had previously been dyed with Inecto.

Each case history is a veritable detective story, at times taxing the powers of observation of both physician and patient. It is obviously impractica-

Fig. 6. Marked dermatitis venenata in a beauty shop operator who was shown to be sensitive to Inecto, red henna, and bronze henna by means of patch tests.

ble to test all of the substances with which a patient may come in contact. It is a serious error, however, to disregard any substance simply because it has not been reported previously as a cause of dermatitis. Assisted by a careful history and an intelligent clinical examination, the patch test is invaluable in determining the etiology of many eczematoid eruptions. It is just as much the duty of the physician to prevent recurrences of a disease as it is to treat the present attack. In the case of the eczematoid eruptions as with most other diseases, an understanding of the etiology is the indispensable factor in preventing such recurrences.

SUMMARY

1. The advantages of the patch test in determining the etiology of certain cases of dermatitis are mentioned, together with a description of the method of applying the test.

2. Twenty-four cases of eczematoid dermatitis are reported, some of them in detail, in which the etiology was established by means of the patch test.

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Some Observations Concerning a Possible Insulin-Inhibiting Substance in Urine*†

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RECENT investigations have pointed to the existence in the blood of a substance which is capable of inhibiting the activity of insulin. Karelitz, Cohen, and Leader,[1] as the outcome of an attempt to discover the cause of insulin resistance in a patient with diabetes mellitus, observed that the blood of diabetics, and to a lesser extent that of normal persons, apparently possessed something which was antagonistic in its action to insulin. While this inhibiting property was demonstrated by blood plasma, it was exhibited to a more marked degree by laked red blood cells. Their data were elicited by studying the blood sugar of rabbits before and after the subcutaneous injection into these animals of mixtures of blood and insulin.

The practical significance of these observations is as yet undetermined. While they may not warrant the elucidation of any new theory regarding the pathogenesis of diabetes, they at least provide grounds for speculation. The cause or causes underlying the principal manifestation of diabetes, namely hyperglycemia, is by no means thoroughly understood. While it is generally agreed that this disease is the result of a deficiency of active insulin in the organism, the known facts do not conform with the view that in every case there must be a deficiency in the production or output of this hormone by the islet tissue of the pancreas. In fact, Warren[2] refers to an "intriguing group of cases without definite anatomical change in the pancreas or other organs". In his series of 300 diabetic autopsies "the pancreas was available for detailed histological study in 259. Of these, 69 were normal so far as could be determined". Cases of clinical diabetes without a pathological background have baffled the pathologist and mystified the clinician. Surely such cases invite an explanation and anything which might throw light upon this dark corner of medicine should be welcome. Unfortunately, short of a postmortem examination, there is no means of distinguishing those cases which possess anatomical changes from those which do not. According to existing knowledge, there is as much, if not more, justification for explaining the latter type of case on the grounds of insulin inhibition as in any other way.

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Accepting the feasibility of neutralization of insulin within the blood stream, the exact nature of the substance or substances responsible for the phenomenon is unknown. Karelitz et al,[1] as a result of their experiments, concluded that the inhibiting agent was probably enzyme-like in character and suggested that it might be trypsin. Their assumption was based partly upon the fact that trypsin is known to inactivate insulin and partly upon their own observations that the insulin-inhibiting property of blood could be diminished or destroyed by heating the blood preliminary to the addition of the insulin. If their conjecture be true, it must be assumed that trypsin is present in the blood of normal persons and that its concentration is increased in diabetes thus accounting for the greater inhibitory effect of diabetic blood. Mauriac and Aubertin[3] had reported previously the antagonistic action of diabetic and normal blood plasma and cells upon insulin action. They believed that a so-called anti-insulin substance resided within the red blood cells and that it diffused from there to the plasma. They also advanced the idea that possibly in some cases of diabetes the permeability of the cells was increased thus allowing more anti-insulin to enter the plasma. Epstein and Rosenthal,[4] as an outcome of some experimental observations on animals, proposed the "trypsin theory" as a possible explanation of certain clinical cases of hyperglycemia and glycosuria. The gist of their contention is that under certain conditions changes in the permeability of the endothelium of the blood capillaries of the pancreas occur, as a result of which the secretory products of the acini, particularly trypsin, gain access to the blood stream. Since the islets and acini of the pancreas possess a common blood supply, opportunity is provided for immediate contact of internal and external pancreatic secretions, hence neutralization of insulin by trypsin. The same investigators demonstrated also that when trypsin entered the portal blood stream glycogenolysis in the liver resulted.

Present Investigation

Realization of the fact that further work along these lines is necessary before any practical application can be made of the above-mentioned contributions led to the idea that some information might be gained from investigating the urine in a manner similar to that which has been used by others in studying the blood, to decide whether or not the insulin-inhibiting factor passes from the blood stream into the urine. If such excretion does occur, provision thus might be afforded for learning something of its nature and properties when separated in a natural way from the proteins of the plasma.

If the blood does contain some soluble substance, enzymic or otherwise, capable of influencing insulin in the manner indicated, it is reasonable to surmise that its presence should be manifest in the urine. Therefore, the first requisite in pursuit of the problem would be to ascertain whether or not urine does show any evidence of insulin-inhibiting effect; if so, whether this is more pronounced with the urine of diabetics than with that of nondiabetics, and finally to attempt to gain

some information regarding the nature of this phenomenon.

At the outset, the undertaking is beset with difficulties and the opportunities for fallacious results and conclusions are numerous. However, the findings thus far have proved sufficiently enlightening to warrant the presentation of this preliminary report, the details of which follow.

Methods of Investigation

One c.c. of a solution containing one unit of insulin per c.c. was added to 5 c.c. of urine. After incubating at 37°C. for thirty minutes the mixture was injected subcutaneously into the flank of a rabbit which had received no food during the preceding twelve hours. As control tests, 5 c.c. of normal saline solution were used in place of the urine. Samples of blood for estimations of the blood sugar were obtained from the marginal vein of the rabbit's ear immediately before and at intervals of one, two, and three hours after the injection. The method used for estimating the blood sugar was that described by Pickard and Pierce[5] employing 0.1 c.c. of blood.

One complete experiment consisted of one or more tests with saline and insulin to ascertain the normal response of the rabbit to one unit of insulin followed by a test using one unit of insulin with unheated urine from a patient with diabetes; another, using one unit of insulin with a sample of the same urine after it had been heated; and still another test, using one unit of insulin with urine from a non-diabetic hospital patient who was not acutely ill, or from a normal person. During the conduct of an experiment as outlined above the same animal was used throughout. A different rabbit was used for each similar set of tests.

In the majority of cases, the urine employed was that excreted during the early part of the day before breakfast and in the case of diabetics before the morning dose of insulin had been administered. Instructions were given for the individual to empty the bladder immediately upon awakening in the morning. This urine was discarded so far as the purpose of the present investigation was concerned. About one and one-half hours later, the specimen for the test was obtained by voiding or, as in the case of adult female patients, by catheterization. By using the morning urine after a preliminary emptying of the bladder it was hoped to avoid the effect of any excreted insulin which might have escaped from the circulating blood during the night in insulin-treated diabetics. Also, by having the specimens secured at that time it was thought that a more constant and comparable concentration of the urine might be obtained. The series of cases under consideration does not include any patients with infections since it is known that infection in some way depresses the effectiveness of insulin. Routine examinations were carried out on all specimens of urine before use and any that were found to contain protein, pus, or blood cells were discarded. The presence of sugar or acetone in the specimens appeared not to influence the results as evidenced by control tests with solutions containing amounts of these substances comparable with those in the urine samples. For the purpose of non-dia-

betic controls, specimens from persons of similar sex and age as the individual diabetics were employed.

In order to test the effect of temperature upon the urine with regard to its insulin-inhibiting property, a portion of each sample of diabetic urine was heated in a water-bath. In some instances, it was subjected to a temperature of from 55° to 60°C. for from three to eight hours. In others, it was placed in boiling water for from five to twenty minutes. After the heating and subsequent cooling, any depletion in volume was made up by the addition of distilled water. The specimen was then kept at ice-box temperature until the next morning when the test with insulin was carried out in exactly the same manner as with the unheated urine.

In consideration of the importance of reaction conditions on the activity of insulin, the reaction of each sample of urine was adjusted to pH 6.4 before the addition of the insulin. This figure happened to be the reaction of the saline solution used throughout these experiments and for that reason was adopted as the standard.

In view of the relative inconstancy of the blood sugar concentrations of fasting rabbits and of their response to one unit of insulin, the method of expressing the results for purposes of comparison was that employed by Culhane[6] in the assay of insulin. According to this method, the blood sugar concentrations at one, two, and three hours were added together and the sum of these divided by three to obtain the average level of the blood sugar following the injection. The resulting figure was then subtracted from that representing the blood sugar immediately preceding the injection. The difference was finally expressed in percentage of the original blood sugar finding. This gives what is referred to as the percentage fall of the blood sugar.

Results

The basis of this report consists of the results obtained in twenty-five complete experiments as referred to above; each consisted of four parts, making in all 100 individual observa-

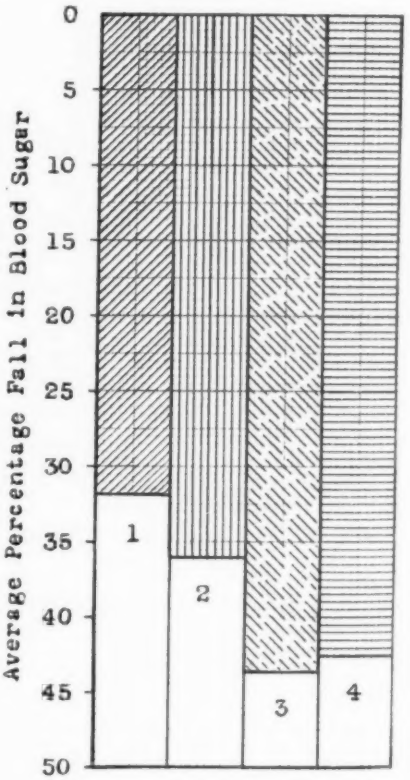

Fig. 1. Comparison of the average percentage fall in the blood sugar of rabbits following the injection of one unit of insulin and 5 c.c. of (1) unheated diabetic urine, (2) non-diabetic urine, (3) heated diabetic urine and (4) normal saline solution.

tions. Whereas no indisputable conclusions can be drawn from such a relatively small number of tests, some points of interest evolve from an analysis of the findings. As might be expected in an investigation of this kind, some discrepancies were encountered but comparison of the various parts of the experiments considered as groups yields some rather definite results.

By assembling all the data into four groups and comparing the average percentage fall of blood sugar thus obtained with unheated diabetic urine, heated diabetic urine, non-diabetic urine and saline as depicted in figure 1, it is seen that diabetic urine causes the greatest amount of insulin inhibition, non-diabetic rather less, and heated diabetic urine none at all as compared with the saline controls. Consideration of the series as a whole suggests at least some differences in the effects of the various test substances upon insulin action. Further comparisons reveal the nature of the tendencies. Reference to table 1 shows that the fall in blood sugar following the injection of unheated diabetic urine and insulin was less than that obtained with similar amounts of normal saline and insulin in twenty out of the twenty-five experiments (80 per cent). The fall was greater in four cases (16 per cent) and showed no difference in one case (4 per cent). In every experiment the decline in the blood sugar was greater with the diabetic urines which had been heated than with the unheated portions of the same samples, indicating more marked insulin effect in the former or, in other words, destruction of the insulin-inhibiting factor by heat. The urine of non-diabetic hospital patients and of normal persons was capable apparently of causing at least slight inactivation of insulin. In eighteen cases (72 per cent) the fall in blood sugar was less with non-diabetic

TABLE I

Observation	Number of cases	Per cent
Fall in blood sugar with unheated diabetic urine and insulin *less* than with normal saline and insulin	20	80
Fall in blood sugar with unheated diabetic urine and insulin *greater* than with normal saline and insulin	4	16
Fall in blood sugar with unheated diabetic urine and insulin the *same* as with normal saline and insulin	1	4
Fall in blood sugar with unheated diabetic urine and insulin *less* than with heated diabetic urine and insulin	25	100
Fall in blood sugar with non-diabetic urine and insulin *less* than with normal saline and insulin	18	72
Fall in blood sugar with non-diabetic urine and insulin *greater* than with normal saline and insulin	6	24
Fall in blood sugar with non-diabetic urine and insulin the *same* as with normal saline and insulin	1	4
Fall in blood sugar with unheated diabetic urine and insulin *less* than with non-diabetic urine and insulin	15	60
Fall in blood sugar with unheated diabetic urine and insulin *greater* than with non-diabetic urine and insulin	9	36
Fall in blood sugar with unheated diabetic urine and insulin the *same* as with non-diabetic urine and insulin	1	4

urine than with saline. It was greater in six cases (24 per cent) and showed no change in one (4 per cent). The fall was less with diabetic urine than with non-diabetic urine in only fifteen instances (60 per cent). It was greater in nine cases (36 per cent) and the same in one (4 per cent).

With regard to the degree of severity of the diabetes in relation to inhibition of insulin by urine, there appeared to be some difference, although not pronounced, between the effect of urine from cases labelled severe and those classified as mild. Urine from the severe cases did tend to exhibit more marked inhibitory effect upon insulin than did that from the so-called mild cases.

It would appear from the data presented above that urine probably does contain a thermolabile substance which has an antagonistic influence upon insulin activity although its existence is not proved. While this substance appears to exist in the urine of non-diabetics it seems to be present in slightly greater concentration in the urine of diabetics. Since it has been shown by others that a thermolabile insulin-inhibiting agent is present apparently in blood plasma[1,3] it would seem reasonable to assume that the substance in urine which is responsible for somewhat similar effects is the same as that which is present in the blood.

Discussion

The only evidence in favor of an enzyme-like character of this special urinary constituent is its behavior toward heat. A more detailed study of its properties is in progress. While it may be trypsin or trypsinogen no unmodified claim is made to that effect. As a matter of fact, the balance of evidence is rather opposed to such a view. Trypsin is a powerful proteolytic enzyme and normal blood contains probably only a very small amount of it in the active state owing to the presence of anti-trypsin. Of the pancreatic enzymes, diastase is found in urine normally but trypsin and lipase are believed to appear there only under special conditions. Trypsin is present chiefly as trypsinogen, especially abundant after a meat diet.[7] Wago[8] found that following the intravenous injection of pancreatin into rabbits the proteolytic pancreatic ferment was excreted rapidly and abundantly into the urine. Thus it is seen that it is possible for trypsin or trypsinogen to gain access to the urine under certain conditions. Its concentration there, apart from the factors which influence the concentration of the urinary constituents in general, might depend upon an increased trypsin content of the blood or diminished production of anti-trypsin. In this regard it should be mentioned that Iacono,[9] in investigating the external secretions of the pancreas in the blood of diabetics, found that the trypsin content did not show any appreciable change over that of non-diabetics.

There are still other avenues of speculation. For example, Loewi[10] has described a hormone-like substance called glycemin believed to be formed in the liver which interferes with the utilization of glucose by the tissue cells. The existence of this substance is, however, problematical.[11] Then there is the possibility of the absence or

deficiency of some complement or coferment which may be necessary for insulin to exert its full effect. But as pointed out by Karelitz and his coworkers,[1] acceptance of this conception implies inadequacy of these factors in normal blood in vitro and still more marked inefficiency in diabetics.

It has been suggested that normal urine contains insulin[12,13] but the contention has been refuted by Lawrence.[14] Lessened insulin content of diabetic urine could hardly explain the limited drop in blood sugar when standard amounts of the urine and insulin are injected into rabbits. If such be the case, however, heating the urine should not cause a more marked fall in blood sugar as compared with the effect of unheated urine. Also, if normal urine contains active insulin, the effect of this plus that which is added should result in a more marked fall in blood sugar than in the case of the saline controls. Actual observations prove these suppositions to be untenable.

There is still to be considered the possible influence of some chemical or bacterial constituent of urine upon the activity of insulin. It has been shown that insulin can be inactivated by ammonium hydroxide and other alkalies[15] but estimations of ammonia in the various specimens both before and after heating indicate that variations in this constituent were not the cause of the differences observed in the specimens with regard to insulin effect. Certain bacterial and chemical toxins, e.g., diphtheria toxin and histamine, are reputed to have a deleterious influence upon the activity of insulin.[16,17,18] It is a matter of practical experience that diabetics do badly in the presence of infection. It is uncertain as yet exactly how infection exerts its influence in these cases, whether it is a matter of direct neutralization of insulin by the toxins produced by the bacteria, the elaboration of some chemical substance possessing anti-insulin properties, for example, some protein-split product, the passage into the blood stream of trypsin as the result of altered permeability of the endothelium of the blood vessels of the pancreas as suggested by Epstein and Rosenthal,[4] or whether it is due to stimulation of certain glands of internal secretion, whose products are antagonistic to insulin such as the thyroid and the adrenals as favored by Lawrence and Buckley.[17] The possible influence of some of these factors has been discussed already but with regard to the effect of any bacteria in the samples of urine employed in these tests, gross contamination was not permitted. On several occasions, cultures were made from the sediment of the centrifuged samples and suspensions of the organisms obtained by washing the surface of the media with normal saline. To these concentrated suspensions, insulin was added and injections made into rabbits in the same manner as in the tests described above. While there was evidence of slight insulin inhibition it was obvious that the presence of any bacteria or bacterial toxins ordinarily present in the urine could not account for the whole of the inhibitory effect exhibited by urine. This is rather in agreement with the findings of Sweeney[19] who concluded that toxemia produced by diphtheria toxin in animals had little, if any, effect upon the action of injected insulin. His deduction was

that toxemia influenced carbohydrate metabolism by impairment of the animal's ability to store carbohydrate due to a suppression of the production of endogenous insulin.

The observation that insulin inhibition was more evident with diabetic urine than with non-diabetic urine in certain cases, but not in all, calls for some comment. Undoubtedly this substance, whatever it is, which is responsible for the inhibitory effect is an elusive body. If it is representative of something in the blood which has a pathogenic influence in certain diabetics, as pointed out above, there is reason for believing that it would operate to a greater degree in some cases than in others, and there is as yet no sure way of identifying the cases in which it would be most likely to be encountered in blood or urine.

Summary and Conclusions

1. A relatively small series of observations points to the presence of a substance in urine which causes partial inactivation of insulin when the latter is added to the urine, incubated and the effect of the insulin upon the blood sugar of the rabbit noted following subcutaneous injection of the mixture.

2. The urine of diabetic patients appears to possess the insulin-inhibiting property to a slightly greater degree than does the urine of non-diabetic hospital patients and normal persons. The difference is most marked in patients with severe diabetes.

3. This insulin-inhibiting factor is destroyed by heating the urine at 60°C. for several hours or by boiling the urine for a few minutes previous to the addition of the insulin.

4. It is assumed that this substance enters the urine from the blood stream by elimination through the kidneys. Whether or not it is identical with the insulin-inhibiting substance which is believed to exist in the blood of diabetics and of non-diabetics is undetermined.

5. The possible significance of the phenomenon relative to the pathogenesis of diabetes mellitus is discussed.

6. While no definite statement can be made concerning the nature of the insulin-inactivating principle in urine, its behavior with regard to heat suggests an enzyme-like character.

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Observations on Human Adrenals with Especial Reference to the Relative Weight of the Normal Medulla*

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DESPITE the immense amount of work that has been done on various problems that have to do with the suprarenals, the question as to the weight of an average, fresh, normal gland still remains in doubt and no figures whatever are as yet available as to the weight of its medulla. Now to be sure, insofar as the first question is concerned, it is possible to set up a tentative average value by means of data to be found in the literature of the subject. For example, this can be done simply by combining the figures contained in the papers of Dietrich and Siegmund[1] and Materna.[2] This procedure, which brings together the experimental results of fourteen workers, yields a mean value of 12.3 grams for both adrenals or a value of slightly more than 6 grams for a single gland. However, it would appear that this figure is much too high. For Materna,[3] on weighing presumably normal suprarenals secured from the bodies of twenty-five persons who had suffered violent deaths—eleven were those of suicides—found that the average weight of a single gland was approximately 4.5 grams; whereas with glands removed from forty pathological subjects, he[4] obtained the following average values for the left adrenal: in twelve cases in which death had been caused by various circulatory conditions, 5.8 grams; in twenty average hospital autopsy subjects, 6.2 grams; and in eight subjects with various septic diseases, 8.4 grams. Having found experimentally that more or less profound changes in the normal relation of the watery and lipoid elements of the suprarenal gland are characteristic of certain disease processes, Materna believes that this variable factor is chiefly responsible for the seemingly discrepant weight findings just described.

In regard to the second question—that as to the weight of the normal medulla—it should perhaps be stated in passing that Elliot and Tuckett,[5] by means of planimeter measurements made with serial sections, determined the amount of medullary tissue in the left suprarenal glands of two rats and found that the medulla formed 9 per cent of the gland in a male rat of 120 grams, and 6 per cent in one of 190 grams; and that Donaldson,[6] who examined by a similar method the supra-

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renal glands of seventeen albino rats, got a mean value of 8.4 per cent for the ratio of the volume of the medulla to that of the whole gland.

Such, it would seem, are some of the principal facts now available as to the two points under consideration.

In this paper a brief account is given of various data obtained during an experimental study of human adrenal glands. However, the main object in view was to determine if possible the relative mass of the normal medulla by dissecting it out and weighing it as a separate structure.

Material

All of the data used in the preparation of this paper were obtained in the autopsy department of a coroner's office, by means of postmortem examinations carried out among the unknown dead of a large city. These examinations were made from three to five times weekly during a period of nearly five months.

In the great majority of cases the subjects utilized were those of persons who had met death suddenly through violence of some sort—for example, in automobile accidents or through falls, blows, crushing injuries, or gunshot wounds. However, in five instances accidental drowning was the cause of death and there were a few cases of suicide. In all nearly 100 pairs of glands were examined. Since, for reasons that will appear later, occasionally it seemed advisable to reject suprarenals obtained from subjects that appeared to be normal and since, for comparative purposes, many of the glands examined were those found in the presence of various pathological states such as occur, for example, in cardio-renal disease, in pneumonia or in septic infections only fifty pairs of glands are included in our series.

In regard to the question as to the sex factor, it may be stated that of the fifty normal subjects, forty-one were males and nine were females. The question as to the age factor cannot be answered definitely. However, the estimated age values of the fifty normal subjects ranged from seventeen to sixty-two years and gave an average of 39.7 years.

The general findings made in the course of this study have now to be considered. As several kinds of data must be dealt with, it will be convenient to describe in the following pages (1) certain factors that appear to modify the shape of an adrenal gland, (2) some data obtained by micrometer measurements, (3) the isolation of the medulla, and (4) the experimental results.

Factors that Modify the Form of the Suprarenal Gland

Subcapsular Location of the Gland. Bartlett[7] described this as "a rare condition in which the adrenals lie in part or entirely in direct apposition with the kidney parenchyma with no intervening capsule". In his case both of the adrenals were firmly adherent to the kidneys though this condition was more marked on the right than on the left side. He found that the right suprarenal measured 45 mm. vertically by 50 mm. in width at its widest part. As both glands were to be examined histologically, they were not weighed.

Other cases of subcapsular location of the suprarenals have been reported

by Apert and Vallery-Radot[8] and by Omelskyj.[9] Having observed heterotopia of the suprarenal in the kidney no less than four times, Omelskyj remarks "that in comparison with the frequency of this phenomenon it is astounding how rarely it is mentioned in the literature". Regarding the question as to what portion of the adrenal surface is prone to unite with the kidney substance, he noted that in each instance the adrenal was attached only at its under extremity. Many of these glands, he states, appeared to be very much enlarged.

Two cases of unilateral, right adrenal-renal heterotopia were examined in the course of this study. The bodies of the subjects concerned were those of powerfully built men who had suffered violent deaths apparently while in a state of perfect health—in one case from a fracture of the skull, in the other from a penetrating wound of the throat. In each instance the lower extremity of the right suprarenal was embedded to the depth of several millimeters in the substance of the kidney; so firm indeed was the union between the two tissues at this point that the gland could be separated from the kidney only by cutting deeply into the parenchyma of the latter organ. These glands were unusually large and in each one the tissue seemed to be thinned out in places. They were extremely bizarre in shape. Neither one is included in the normal series listed in table 1. Expressed in millimeters, the length and width measurements of the two glands were, respectively, 69 by 46, and 45 by 55. In grams, the weights of each whole gland and its medulla were, respectively, 7.029–.765 and 6.475–.740.

On the whole, such as it is, the foregoing evidence seems to indicate that, when it is adherent to the kidney, the suprarenal gland gradually becomes pulled out of shape and enlarged—particularly in its transverse measurement. It may be added, as of some interest in this connection, that no distortion of the suprarenal was noted in those cases—and this condition was encountered a number of times—in which the gland was firmly united with the under surface of the liver.

Absence of One Kidney. This appears to be a rare condition. Guizzetti and Pariset[10] found that one kidney was absent in 39 out of 20,000 autopsies. However, the statistics as to the incidence of this condition vary widely. Other authorities assign values that run as high as 1 in 4,000. Usually it is the left kidney that is missing.

What effect does the absence of one kidney have upon the shape of the corresponding suprarenal gland?

Miloslavich[11] answers this question by stating that, in such a case, the suprarenal is rounded in form and that neither of its surfaces exhibits the indentations and longitudinal ridges that usually characterize this gland. It is not to be denied, he affirms, that under normal circumstances the kidney and the liver offer a resistance to the suprarenal that probably exerts some influence upon its configuration. However, his paper contains no autopsy data obtained from cases of renal aplasia.

In a case of absent left kidney de-

FIG. 1. Normal adult adrenals photographed in the fresh state. Note pressure-ridge on each one.

scribed by Lucksch[12] the left adrenal was rounded in form and exhibited none of the usual surface markings. It measured 38 by 35 millimeters. The two glands weighed in the fresh state 10.5 grams. Curiously enough they were joined together by a narrow isthmus.

Congenital absence of the left kidney was noted in one of the normal cases reported in this paper. The cadaver in question was that of a bandit, a man in the early fifties, symmetrically developed and athletic in type. The cause of death was a gunshot wound of the heart. In the course of the postmortem examination it was discovered that the left kidney was missing. Otherwise, however, nothing of importance was noted. The right

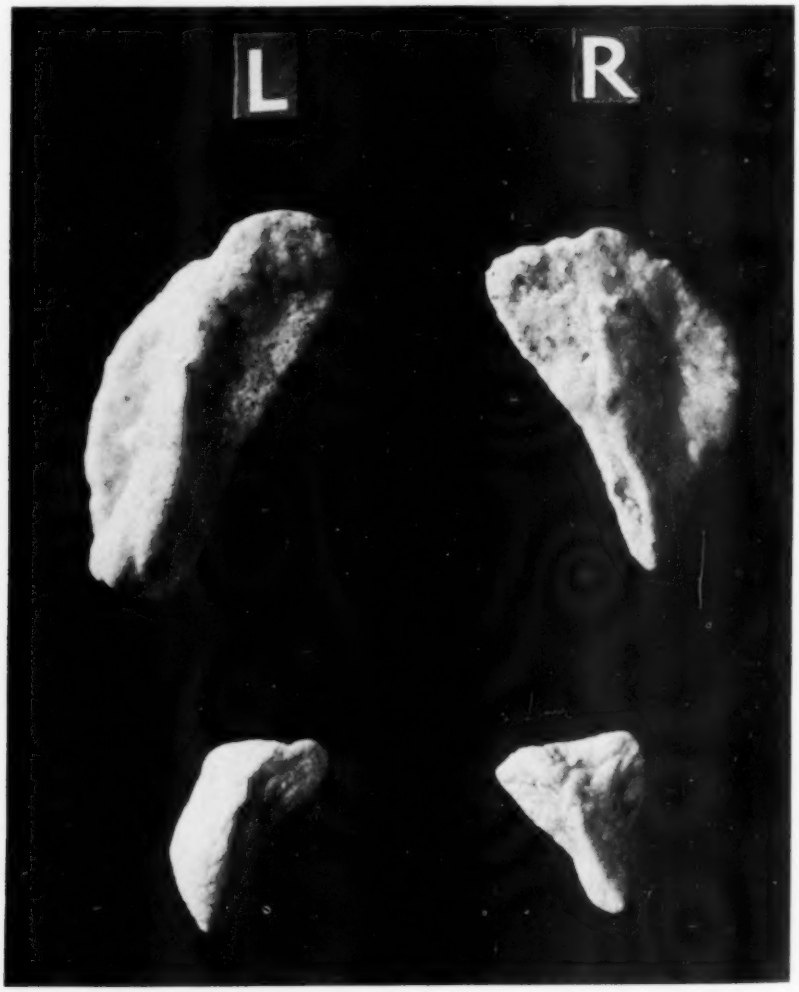

FIG. 2. Adrenals of normal infant four months old compared with adrenals of adult. Measurements of infant's adrenals: left 33 mm. by 9 mm.; right 28 mm. by 22 mm. Weights: left 0.939; right 0.963 gram.

kidney appeared to be perfectly normal. Unfortunately it was neither measured nor weighed. The left suprarenal was in the normal location, concealed—as it usually is—amid layers of fat. When dissected free, it was found to have a rounded, almost disc-like, form and to be almost entirely devoid of surface markings. However, both its color and its consistency were normal. Figure 3 (A-2) shows the medulla of this gland as it appeared after it had been hardened in formaldehyde solution. The other medulla (A-1) is that of an average normal left suprarenal gland. Further details concerning the adrenals of this subject are given elsewhere. (Table 1, No. 6.)

It will be noted that the findings made, both in Lucksch's case and in the one here reported, substantiate Miloslavich's opinion: namely, that when one kidney is congenitally absent the corresponding suprarenal gland is nearly round in shape and almost smooth on both of its surfaces. However, topographically speaking, it may be pointed out that such an unmodeled gland appears to be chiefly remarkable because of the absence of the prominent flange-like ridge that invariably marks the posterior surface of an adrenal when its kidney is in situ. The five pairs of glands shown in figures 1 and 2 give a fair idea as to the form of this ridge and as to its orientation. Incidentally, it should be remarked that these glands were photographed in the fresh state immediately after they had been weighed. It will be observed that the concavity of the ridge faces the inferior border of the gland and that, instead of lying in the principal axis of the gland, the ridge crosses the adrenal obliquely.

The question as to when this peculiar elevation first makes its appearance seems to be unanswerable. But the fact that the ridge is present in typical form in the fourth month of infancy (figure 2), seems to indicate that it must be thrown up at a very early period, perhaps even before the onset of the cortical involution process. Almost equally unanswerable, it would seem, is the query as to how the ridge is formed. In this connection, however, it may be stated that there is some objective basis for the supposition that it is formed by pressure, since fairly numerous measurements made in the course of this study show that the inferior border of an adrenal gland is usually, if not invariably, much thinner than its superior border. This subject is treated more fully in the next section.

Data Obtained by Micrometer Measurements

Before proceeding to describe the measurement data, attention may be called to certain physical peculiarities that appear to be characteristic of normal and of pathological adrenals.

Physical Characteristics of Normal Adrenals. As a prefatory note, it should perhaps be remarked that unless great care is exercised during the autopsy the suprarenals are apt to be cut or torn. So greatly does the normal suprarenal resemble, both in color and consistency, the tissue in which it lies embedded that, even in a laboratory dissection, it was often no easy matter to find the gland in the collop of kid-

ney substance and fat obtained at the postmortem examination. .

Careful notes on the subject kept throughout this study seem to show that in any given case there is no correlation between the size of the adrenals and the grade of physical development. Thus, while it is true that men of outstanding vigor commonly have adrenals that weigh together around 8 grams, it is also true that many strongly built subjects had adrenals that weighed 7 grams or less.

In regard to the question as to the

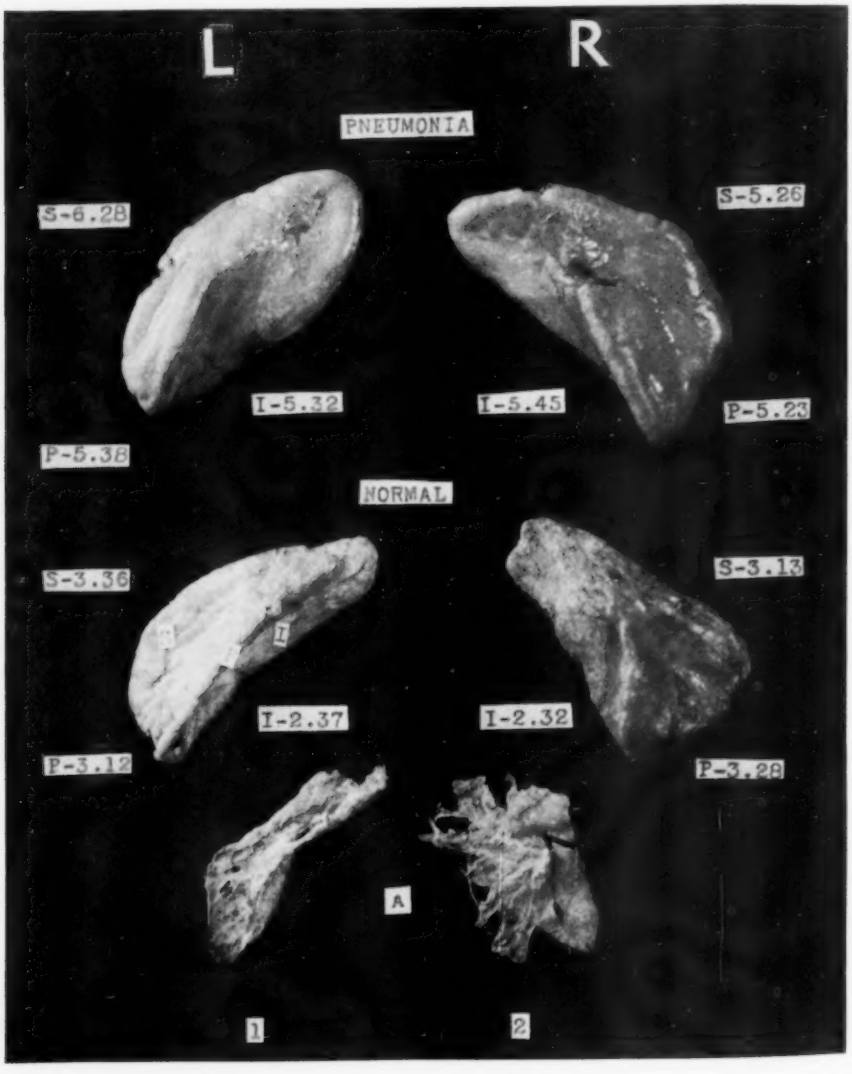

FIG. 3. Normal and morbid adrenals compared. "S"—Superior border. "P"—Pressure ridge. "I"—Inferior border. Pneumonia adrenals weigh 16.0 grams. Normals weigh 6.79 grams. "A"—(1) normal left medulla. "A"—(2) left adrenal medulla in congenital absence of the left kidney.

consistency of a fresh, normal adrenal, it may be stated that such a gland is always limp so that it bends readily over the finger; that it is everywhere soft to the touch; and that its borders as well as its pressure-ridge seem rather delicate and thin. A normal gland is usually brownish-yellow in color. But in two subjects it was noted that the cortical lipoids as well as the abdominal fat were distinctly orange-colored, presumably because of the presence of an excess of carotinoid pigment.

Physical Characteristics of Morbid Adrenals. It seems to be characteristic of the adrenal capsule that it is rather tough to cut, though it tears easily. Hence it may be said somewhat to resemble so-called "dead-rubber". This peculiarity perhaps explains why it is that a suprarenal gland, without exhibiting any very striking changes either in its length or its width, may nearly double in weight. The whole gland appears to swell, as though it had been injected with a fluid of some sort. If this hydration process happens to be minor in degree, there may be nothing remarkable in the appearance of the gland, except that it may seem to have rather thick borders. Extreme grades of hydration, however, produce characteristic changes. The whole gland then has a sodden appearance and its substance feels unusually firm and resistant to the touch. It is often possible to palpate such a gland through the surrounding tissues even though the gland itself cannot be seen. On stripping away the adherent fat from such an adrenal, it will be seen that its surface shows but few of the natural indentations; that its borders, like those of a mattress, are cushioned or "rolled" and that its pressure-ridge is very broad, especially at the base. These changes in the appearance of the suprarenals were noted most commonly in the presence of pneumonia. For example, in five cases of that disease the average length and width measurements of the adrenals were, respectively, 58 mm. and 28 mm.; whereas the average weight value was 16.2 grams.

Measurement Data. Numerous observations having shown that the superior and inferior borders of the suprarenal gland seemed to differ considerably in point of size, in order to find out how great this apparent difference was, some exact measurements were made. The instrument used was a Starrett micrometer. This instrument reads to hundredths of a millimeter. As this work was undertaken at a rather late stage of the investigation, relatively few glands were measured. Twenty were normal glands and four were obtained from pneumonia subjects. Stated in millimeters, the following average values were obtained for the inferior border, the pressure-ridge, and the superior border, respectively: normal adrenals, 1.8, 2.4 and 2.6; pneumonia adrenals, 4.0, 5.0 and 5.6. However, since these measurements show that the difference was a constant one and that it amounted to approximately one millimeter, they appear to establish the fact that the superior border of the adrenal gland is larger than the inferior border. Typical sets of measurements are shown in figure 3. This figure also illustrates very well, as regards their external appearance, the main points of difference between normal adrenals

and those sometimes found in the presence of pneumonia.

Isolation of the Medulla

Preliminary Note. Here the question as to the practicability of such an undertaking will be touched upon and the surface form of the adrenal medulla will be roughly described.

In regard to the first point, the experimental evidence obtained in the present inquiry seems to show that it is possible to isolate the medulla of an adrenal gland by dissection, provided that the two principal tissues of the gland can be separated from one another along a definite line of cleavage. Experience shows that this sep-

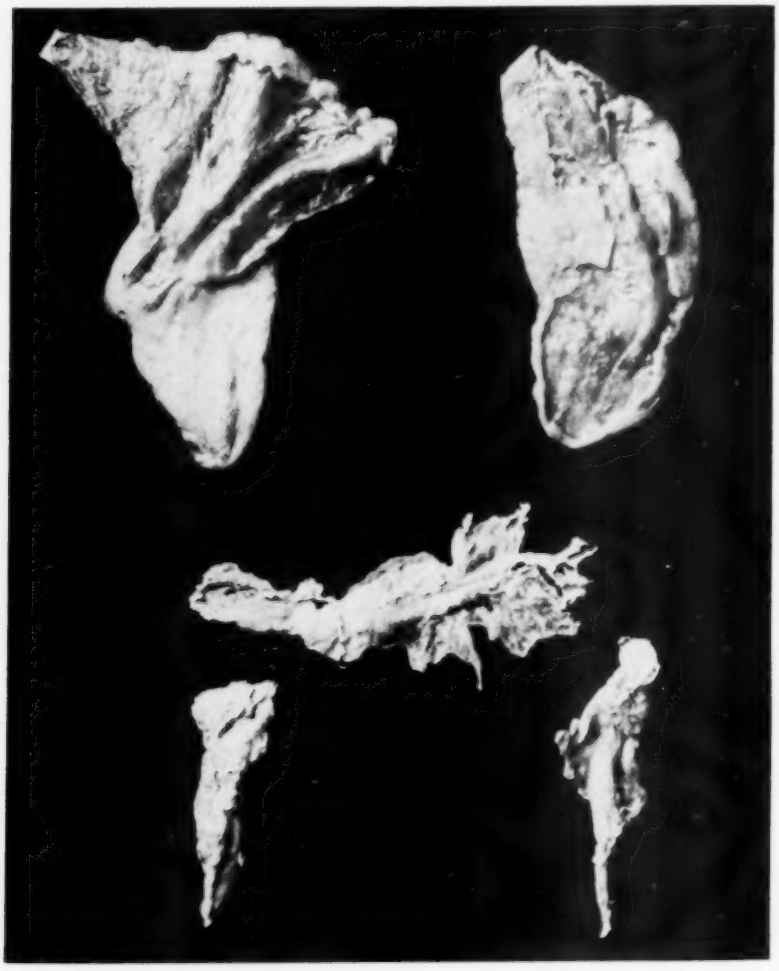

Fig. 4. Normal adrenals laid open to expose the medulla. In left-hand gland note fibrous attachments radiating from tip of medulla to gland border. In right-hand gland the cortex has been partly cut away in order to show arrangement of the medulla. Center figure shows body and membranous portions of medulla. In the two lower figures the membranous portion is curled up from the action of formaldehyde.

aration can be accomplished in about three out of four normal specimens. Naturally, the partition effected is never a quantitative one because of irregularities in the configuration of the medulla. However, with suitable material, it seems probable that the average error is considerably less than 5 per cent.

How is the adrenal medulla arranged within the gland? and what is its general appearance when isolated?

Often simply by inspecting an intact adrenal some idea can be obtained as to the disposition of its medulla. For the surface of a normal adrenal is always marked by irregular elevations (figure 1) and as a rule it is under the most prominent one of these that the main mass of the medulla will be found when the gland is opened. The arrangement of the medulla can also be made out dimly if an adrenal is studied by means of transmitted light. A convenient way to do this is to hold the specimen to be examined up against a 60-watt Mazda light and to observe it through an opening cut in a piece of pasteboard. Under such circumstances, the medullary masses appear as relatively darker areas against a diffuse rosy background.

When it is dissected out and viewed in its entirety, the medulla is seen to consist of two parts—a body and a membranous portion.

Usually the main mass of the body is aggregated about the emergent vein. Its form varies greatly. Sometimes its general shape is that of an Indian arrow-head, but more commonly the body of the medulla is elongated, its length corresponding to that of the pressure-ridge under which it lies. Commonly, too, one of its extremities tapers to a point (figure 4). The posterior surface of the body of the medulla is always convex and as a rule it is marked by a fine, median longitudinal groove. The medulla is soft and delicate in texture. Its color usually is grayish-white.

The membranous portion of the medulla (figure 4) extends outward from the body of the medulla to the borders of the gland. It is found chiefly in those flat, thin areas of the adrenal where the two opposite cortical surfaces are virtually in direct contact with one another. Very thin and traversed by numerous blood vessels, the membranous portion of the medulla is attached at regular intervals to the periphery of the gland by fibrous trabeculae. Commonly its color is the same as that of the bed of brownish pigment in which it lies.

Dissection. Omitting unnecessary details, the isolation of the adrenal medulla is carried out as follows: A gland having been selected and freed from every bit of adherent fat, the summit of its pressure-ridge is opened by an incision that runs throughout its length. Starting about midway of this incision, the thin process of medullary substance sure to be present within the ridge is sought for and when found is cautiously separated from the adjacent cortical tissue with the aid of a scalpel. At the end of this stage of the dissection a thin, longitudinal fold of medullary substance should stand, nearly erect, in the center of the incision. This fold, which may be likened to a dorsal fin, is now followed on down until the convex surface of the main medullary mass is exposed and

TABLE I

Relative weights of normal suprarenal medullae. The weight determinations were made with glands secured from 50 selected coroner's subjects.

	Gland Measurements				Weights in Grams					
	Left		Right		Left			Right		
No.	Length, Mms.	Width, Mms.	Length, Mms.	Width, Mms.	Whole Gland	Medulla	Medulla %	Whole Gland	Medulla	Medulla %
1	55	19	44	27	3.250	.440	13.5	3.620	.495	13.6
2	44	23	47	23	3.160	.369	11.6	3.035	.339	11.1
3	51	24	53	26	4.519	.439	9.7	3.868	.345	8.9
4	45	25	42	22	3.459	.339	9.7	2.899	.345	11.9
5	53	21	56	23	4.651	.511	10.9	4.302	.453	10.5
6	45	33	51	25	4.214	.621	14.7	4.086	.575	14.0
7	58	20	56	27	4.248	.355	8.3	4.012	.375	9.3
8	48	24	54	32	3.950	.425	10.7	4.275	.460	10.7
9	53	19	50	25	3.980	.469	11.7	4.115	.450	10.9
10	49	30	51	29	4.745	.502	10.5	4.608	.585	12.6
11	46	21	32	30	3.310	.260	7.8	3.322	.340	10.2
12	51	24	50	25	3.529	.285	8.0	4.025	.474	11.7
13	55	25	61	20	3.510	.493	14.0	3.405	.472	13.8
14	40	27	59	35	2.819	.318	11.2	3.595	.368	10.2
15	47	22	41	28	3.878	.370	9.5	3.799	.392	10.3
16	58	23	59	27	3.740	.471	12.5	4.119	.568	13.7
17	49	23	54	33	3.179	.368	11.5	3.395	.469	13.8
18	52	23	48	40	4.883	.437	8.9	4.835	.481	9.9
19	50	25	48	23	4.380	.501	11.4	3.970	.415	10.4
20	54	31	49	23	5.355	.449	8.3	4.573	.390	8.5
21	54	25	51	27	5.419	.505	9.3	5.248	.449	8.5
22	50	21	60	22	3.985	.330	8.3	3.780	.342	9.8
23	56	24	49	30	4.965	.490	9.8	3.782	.358	9.4
24	55	30	48	27	4.874	.460	9.4	3.932	.399	10.1
25	53	24	58	23	4.952	.543	10.9	4.798	.505	10.5
26	52	32	58	30	5.424	.430	7.9	5.915	.535	9.0
27	55	21	48	23	4.719	.505	10.7	3.851	.499	12.9
28	42	14	58	31	2.220	.195	8.7	3.615	.370	10.2
29	50	29	50	28	4.365	.505	11.5	4.399	.498	11.3
30	50	21	42	23	3.902	.431	11.0	3.618	.365	10.0
31	64	18	59	32	4.379	.391	8.9	3.848	.402	10.4
32	58	19	68	34	3.329	.275	8.2	4.761	.438	9.1
33	56	25	51	24	4.419	.398	9.0	4.498	.467	10.3
34	48	19	48	22	3.670	.480	13.0	4.435	.454	10.2
35	57	16	38	27	3.753	.540	14.3	3.452	.415	12.0
36	54	22	59	27	3.439	.278	8.0	3.358	.285	8.4
37	49	20	48	24	4.706	.585	12.4	4.712	.672	14.2
38	59	23	52	25	4.055	.385	9.4	4.622	.499	10.7
39	62	22	65	25	4.099	.569	13.8	5.255	.670	12.7
40	63	22	55	29	4.769	.505	10.5	4.923	.451	9.1
41	62	26	57	32	4.649	.420	9.0	4.372	.432	9.8
42	56	28	62	30	4.730	.435	9.1	5.048	.480	9.5
43	60	20	48	28	4.448	.415	9.3	4.406	.448	10.1
44	49	30	49	34	4.204	.429	10.2	4.571	.561	12.2
45	60	26	51	29	5.775	.535	9.2	5.309	.570	10.7
46	72	14	63	21	4.682	.512	10.9	4.473	.455	10.1
47	57	26	51	29	3.934	.410	10.4	4.289	.455	10.6
48	51	26	65	34	4.282	.415	9.6	4.180	.419	10.0
49	58	22	54	23	3.389	.360	10.6	2.738	.325	11.8
50	55	19	50	32	4.103	.398	9.7	4.019	.412	10.2
Means	53	23	52	27	4.165	.431	10.3	4.161	.448	10.7

the dissection is continued until the entire body of the medulla is laid bare (figure 4). The body of the medulla having been fully exposed, the next step is to begin the work of detaching the whole medulla from its bed. In order to do this, after first cutting the fibres that attach it to the extremity of the gland, the pointed end of the medulla is gently separated from the underlying tissue. It is then folded upon itself and this process of separating and folding is continued until the entire medulla, body and membranous portion, has been dissected out, the adrenal vein being severed last of all. The size of this vessel is often out of all proportion to the size of the gland it serves. In some instances it was found to be no less than 5 mm. in diameter.

The detached medulla should be carefully dried with absorbent paper before it is weighed.

Experimental Results

Since they speak for themselves, little need be said with reference to the results exhibited in table 1. It may be suggested, however, that, even though they are not strictly quantitative, the data as to the weight of the medulla are probably accurate enough for most practical purposes.

As a supplementary note, the fact may be mentioned that in eight of the fifty normal cases pigment spots were found in the adrenals. In shape the spots were oval or roughly triangular and from 1 mm. to 2 mm. on a side. The largest spot measured 5 mm. by 1 mm. The color was the same in each instance, i.e., a very dark brown. As regards their location, it seems worthy of remark that these spots always were found precisely in the cleavage plane and broadside on to the medulla; but they were invariably on the cortical side of the contact zone. No pigment spots were found in the medulla.

Conclusions

1. Stated in grams, the weight of a pair of adrenals varied from 5.8 to 11.3. The average value for fifty pairs of normal glands was 8.3.

2. Stated in grams, the average weights of fifty left and fifty right adrenals were, respectively, 4.165 and 4.161.

3. Stated in fractions of a gram, the average weights of fifty left and fifty right adrenal medullae were, respectively, .431 and .448.

4. The medulla appears to form about 10 per cent of the gland.

5. It is pointed out that the superior border of the adrenal gland is larger than the inferior border.

6. Attention is drawn to peculiarities in the configuration of the adrenals that occur (1) in adrenal-renal heterotopia and (2) in congenital absence of the left kidney.

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Bacteriophage Therapy in Bacillary Dysentery of the Flexner Type*†

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Introduction

Since the suggestion was first made that bacteriophage be used as a therapeutic agent, numerous reports have occurred in medical literature concerning its value. Some of them have been favorable in character, and others less certain as to its beneficial effects. Bacteriophage has been recommended for a great variety of conditions and, indeed, possesses the characteristics required of an ideal germicide in that it is harmless to the body tissues and theoretically destroys the pathogenic organisms. This phenomenon of lysis can be demonstrated easily in vitro with young cultures, but it is doubtful if the results obtained in the animal body by the administration of bacteriophage are always equally phenomenal. Its successful use has been most commonly reported in connection with the gram-negative intestinal bacteria, such as *Shigella*, *Vibrio cholerae*, and *Escherichia coli* and with staphylococcic infections, both cutaneous and systemic in character.

Unfortunately, however, many of the clinical reports demonstrate but one side of the picture; for instance, one report states that bacteriophage was used in fifty cases—in forty-two with excellent results, in five with mediocre results, and in three with unsuccessful results. No mention is made of control cases and no statements are given that would indicate how the cases might have progressed if the bacteriophage had not been used.

The present report on the use of bacteriophage in bacillary dysentery of the Flexner type represents the results of one group of bacteriophage studies made at the Los Angeles County General Hospital and at the School of Medicine, University of Southern California, during the last two years. Other studies in progress have to deal primarily with its use in typhoid fever and in staphylococcic infections.

Methods Employed

During the period of these observations more than one hundred cases of bacillary dysentery have been encountered in the Contagious Unit of the Los Angeles County General Hospital. Only sixty-eight cases are included in the data here presented since only those cases were selected for discussion from which it has been possible, first,

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to isolate a bacterium giving characteristic biochemical and serological reactions of *Shigella paradysenteriae*, Flexner type, and, second, to completely lyse the organism isolated with the bacteriophage used in treatment. Cases yielding other strains of bacillary organisms or strains of Flexner type which failed to lyse with our bacteriophage have not been included in this report.

The cases are divided into two groups, first the 1930 series and second the series of patients treated in 1931. In the 1930 series the lytic property of the bacteriophage was tested against each organism isolated before the phage was administered. This caused a delay of several days after admission to hospital before the phage could be administered, since this time was necessary to permit (1) the isolation of the organism and (2) the adaptation of the phage by growth with the organism isolated from the patient.

Since it was found that about 90 per cent of all our Flexner organisms tested were lysed by a single strain of bacteriophage, we decided to employ this strain in the second series and to administer it just as soon after admission as possible. Such administration of bacteriophage immediately after the admission of the patient should be advantageous since it saves the time usually required for routine laboratory procedures in isolation of the organism and for the preparation of the bacteriophage.

Insofar as it was practicable, alternate cases were selected for "phage cases" and for "control cases", care being taken that a phage case and a control case exhibited as nearly uniform symptoms as possible.

The cases receiving bacteriophage were given a minimum of three doses of bacteriophage by mouth at approximately twelve hour intervals. The dose consisted of from 3 to 5 c.c. of the laboratory prepared broth filtrate which was added to a small amount of unheated water before administration.

Both treated and control cases received the same routine symptomatic treatment which consisted primarily of dietary precautions and methods to limit dehydration.

In children, fluids by mouth were withheld or limited for the first twelve or twenty-four hours, normal saline being given intraperitoneally and by hyperdermoclysis, and glucose intravenously. Following this period fluids were gradually added by oral administration, boiled skimmed milk, lactic acid milk, or protein milk and glucose water being alternated every two hours until the patient had improved sufficiently to receive small amounts of solid food in the form of custards, cereals, cottage cheese, etc.

Adult patients usually received their fluids by mouth, parenteral administration seldom being required. Boiled skimmed milk or buttermilk was allowed during the first forty-eight hours, after which other foods were gradually added. Fats were withheld from both children and adults until stools were normal.

Milk of bismuth or bismuth subcarbonate was given to both children and adults when dysentery was especially marked. Paregoric was allowed in event of severe cramps or tenesmus.

though only one patient in this series received it.

Tables and Discussion

In collecting information regarding the cases, special data were assembled concerning the following points: (1) age of the patient, (2) onset and course of the disease prior to hospital admission, (3) temperature, before, during, and after giving bacteriophage, (4) the number and type of stool before, during, and following administration of bacteriophage, (5) special toxic or neurologic symptoms, (6) any unusual complications, and (7) the number of days of hospitalization. The relevant data for comparative purposes are included in the tables.

The number of days of hospitalization has been selected as the most significant criterion for comparison since it represents the most constant standard. It is a general rule that patients with fever are discharged from the hospital three days after a return of the temperature to normal unless other symptoms contraindicate release. In this series of cases the number of stools had also returned to normal before the patient was discharged. Owing to the pressure for admission of patients to the Contagious Disease Unit of the hospital, patients were discharged just as soon as symptoms permitted.

Many mild cases of diarrhea or dysentery caused by bacteria belonging to the genus Shigella occur in this region which never become sufficiently severe for hospitalization. Quite commonly within two or three days the patient recovers without special medical attention. If bacteriophage or any other therapeutic agent were employed in such a group without adequate controls, the results obviously would be interpreted as being favorable. The cases herein recorded, however, represent individuals either who were ill several days at home before coming to the hospital or whose symptoms were sufficiently severe to warrant immediate hospitalization. They, therefore, represent an ideal group for consideration in the testing of any therapeutic measure.

Table 1 gives a summary of the cases treated during the first season when a specific bacteriophage was prepared for each organism. In this series the average number of days elapsing between admission of the patient and administration of the bacteriophage was four. It will be seen that there is no marked difference between the ages, nor between the intensity of symptoms in the group treated with bacteriophage and in the control group; the temperature range, the type of stools, and number of stools per day being about the same in both series. Likewise, the average number of days of hospitalization in each group does not differ markedly, it being 11.9 days for the treated cases and 10.1 for the control series. It is true that the treated cases show a longer period of hospitalization than the control cases, but since bacteriophage was not administered until several days after admission, and since the series was small, it was decided not to lay too much emphasis on the results and to study another series of cases by the second method.

Table 2 gives a summary of the cases treated during the 1931 season when bacteriophage was administered

as soon after admission to the hospital as it was possible to collect a stool from the patient. Organisms recovered from such a stool were later tested for lysis with a portion of the bacteriophage employed and only those cases are recorded in this table where complete lysis occurred. In this series, as well as in the first series, the ages and fatal cases died during the first twenty-four hours of admission, two having received bacteriophage and one being a control, it seems fair to consider that these reached the hospital too late for any treatment to be of value. The other four fatal cases, two treated and two controls, were of approximately equal intensity. One of the control

TABLE I
SERIES 1930
Table showing Results of Treating Cases of Bacillary Dysentery with Bacteriophage.
(Bacteriophage tested for lysis before administration)

Treated by Bacteriophage given by mouth						Controls					
Patient Number	Age	Maximum Temperature	No. of Stools	Type of Stools	Days in Hospital	Patient Number	Age	Maximum Temperature	No. of Stools	Type of Stools	Days in Hospital
1	1	103	F	Dys.	18	13	2	101	N	Dys.	4
2	3	102	F	Dys.	16	14	2	104	M	Dys.	10
3	1	103	F	Dys.	14	15	2	103	M	Dys.	14
4	2	101	F	Dys.	11	16	4	103	N	Dys.	11
5	2	101	M	Dia.	4	17	7	106	F	Dia.	20
6	3	104	N	Dys.	10	18	9	102	F	Dia.	14
7	3	103	N	Dia.	14	19	12	101	M	Dia.	18
8	5	103	N	Dys.	17	20	18	100	M	Dia.	3
9	5	100	M	Dia.	10	21	22	100	F	Dys.	4
10	6	102	M	Dys.	8	22	57	99	F	Dys.	4
11	21	100	N	Dys.	9						
12	67	101	M	Dia.	10						
Average Days of Hospitalization 11.9											10.1

M (moderate) 4-6 per day; F (frequent) 6-10 per day; N (numerous) 10 per day; Dia—Diarrheic; Dys—Dysenteric (Blood and mucus).

clinical manifestations of the patients in the treated and control groups compare favorably. It will be noted that the average period of hospitalization of the treated group is eleven days, while in the untreated or control group it is 12.1 days, there being a difference of 1.1 days between the two groups.

Though there were no deaths in the 1930 series, there were seven in the 1931 series, four among those treated with bacteriophage and three in the untreated series. Since three of the cases died in two days as did one of the treated cases, while the other control case died in five days and the other treated case in eight days. It is recognized that the number of fatal cases is too small to be of significance but since there is little difference in the fatalities in the treated and untreated series, significant affirmative evidence for the therapeutic value of bacteriophage is lacking.

D'Herelle, in 1917, first called attention to the presence of a substance

lytic for dysenteric bacteria after having isolated this substance from the stool of a patient convalescing from bacillary dysentery of the Shiga type. In 1926, he further cites in detail several cases of bacillary dysentery of the Shiga type and shows that bacteriophage lytic for the Shiga bacterium is commonly present in association with the organism. It is suggested that fatalities result from a failure of the bacteriophage to exert a destructive action on the specific bacteria, and it is assumed that lytic action of a bacteriophage assures protection.

With this possibility in mind, some have accepted bacteriophage as a desirable treatment for bacillary dysentery, especially in those regions where the disease is common in epidemic form. A number of the earlier reports indicated favorable results from its use therapeutically, and with due consideration to these findings the present

TABLE II
SERIES 1931
Table Showing Results of Treating Cases of Bacillary Dysentery with Bacteriophage.
(Bacteriophage given upon admission and then tested for lysis)

Treated by Bacteriophage given by mouth						Controls					
Patient Number	Age	Maximum Temperature	No. of Stools	Type of Stools	Days in Hospital	Patient Number	Age	Maximum Temperature	No. of Stools	Type of Stools	Days in Hospital
23	1	101	F	Dys.	19	42	1	100	N	Dys.	29
24	1	104	F	Dia.	9	43	1	102	F	Dys.	8
25	1	106	F	Dia.	9	44	1	105	F	Dys.	9
26	1	102	F	Dys.	14	45	2	102	M	Dia.	8
27	2	102	F	Dia.	10	46	2	102	M	Dia.	20
28	3	104	F	Dys.	5	47	5	103	N	Dys.	5
29	3	102	M	Dia.	13	48	3	100	N	Dys.	3
30	4	100	F	Dia.	5	49	3	102	F	Dys.	19
31	4	104	F	Dia.	7	50	3	105	F	Dia.	12
32	4	103	N	Dys.	19	51	1	104	F	Dys.	18
33	4	101	F	Dys.	19	52	5	104	F	Dys.	20
34	5	103	F	Dys.	19	53	5	103	F	Dys.	15
35	6	104	N	Dys.	3	54	6	104	F	Dys.	21
36	7	102	N	Dys.	20	55	7	102	N	Dys.	9
37	19	102	N	Dys.	8	56	9	104	F	Dys.	9
38	20	101	M	Dia.	6	57	20	104	F	Dys.	13
39	20	100	M	Dia.	4	58	30	99	M	Dys.	6
40	26	102	F	Dia.	7	59	32	100	M	Dia.	5
41	41	100	N	Dys.	13	60	47	100	M	Dia.	11
						61	63	101	M	Dia.	12
Average Days of Hospitalization 11						Average Days of Hospitalization 12.1					
Average Days of Hospitalization (1930) 11.9						Average Days of Hospitalization (1930) 10.1					
Average of Both Series 11.45						Average of Both Series 11.1					
FATAL CASES—1931											
62	1	105	N	Dys.	2	66	1	104	F	Dia.	2
63	1	104	N	Dys.	8	67	3	106.6	N	Dys.	1
64	4	105	F	Dia.	1	68	5	106	N	Dys.	5
65	4	106	N	Dys.	1						

study was begun. During its progress a number of recent papers have come to our attention and brief summaries of some of these may be mentioned.

Compton (1929) reports the use of bacteriophage in 66 cases and states the results were very good in 35 cases, good in 10, medium in 6, and a partial failure in 10. He cites no controls in his series.

Burnet, McKie and Wood (1930) in an investigation of 21 cases found that the presence of a highly active phage was generally of favorable import for the patient, though in children of over one year the presence or absence of bacteriophage was not of prognostic significance.

Sen (1930) reports decided success in the treatment of children by bacteriophage.

Asheshov, Taylor, and Morison (1930) in a summary state that in Shiga and Flexner types of bacillary dysentery no effect on the disease is traceable to the administration of bacteriophage. Morison does state, however, that in three epidemics he had 15 deaths in 57 treated cases, and 50 deaths in 92 untreated cases.

London (1930) administered bacteriophage orally to 141 cases of bacillary dysentery; 129 were cured and 12 died. Here again no controls were mentioned.

Riding (1930), in recording the results of 48 cases in which lysis of the organism isolated from the patient was apparent, concludes that bacteriophage is probably quickly eliminated or destroyed and that the clinical course of acute bacillary dysentery is not altered by the oral administration of bacteriophage. He used some of his cases for controls.

Taylor, Greval, and Thant (1930) report a series of 20 controls and 26 cases given 2 c.c. of bacteriophage three times a day and conclude that, in spite of the presence of phage of higher activity in the stools of treated cases as compared with controls, no significant difference exists in the progress of cases either in regard to effect on mortality or as to duration of the period of attack. It is of interest to note that they draw similar conclusions from their controlled series of cholera cases treated with bacteriophage.

Results of the study here reported do not differ from the conclusions of the workers just mentioned who used untreated control cases for comparison. In our series 68 cases are recorded, 35 who received bacteriophage by mouth in addition to symptomatic hospital treatment, and 33 cases who did not receive bacteriophage. The severity of symptoms and ages of patients in the two series compare favorably. It was found (1) that there were four deaths in the bacteriophage treated group and three deaths in the control series and (2) that the average days of hospitalization per patient in the bacteriophage series is 11.45 days while in the control group the average period is 11.1 days.

Conclusions from this study indicate that the oral use of bacteriophage in bacillary dysentery of the Flexner type by the methods here employed does not alter the clinical course of the disease, does not appreciably reduce the number of days of hospitalization, and does not lower the death rate. Continued studies in which larger and more frequent amounts are being given orally in conjunction with bacterio-

phage by retention enema are in progress.*

Summary

1. Sixty-eight cases of bacillary dysentery from which *Shigella paradysenteriae* of the Flexner type was isolated are considered in a study of bacteriophage therapy.

2. Thirty-three of the cases received no bacteriophage and are therefore used as controls.

3. Twelve of the treated cases appeared in the 1930 season when a specific bacteriophage was prepared for each case. Such phage was administered by mouth, an average of four days after admission to hospital. The average number of days of hospitalization of this group was 11.9 days while in the control group for the same period the average was 10.1 days. No deaths were recorded in either series during this season.

4. Twenty-three cases in the 1931 series received a bacteriophage which was later tested for lytic properties. Such bacteriophage was administered by mouth within a few hours after admission to hospital. The average number of days of hospitalization of this group was 11 days while in the corresponding control group, the average period of hospitalization was 12.1 days. There were four deaths in the bacteriophage treated series and three in the control series during this season.

5. These results indicate that the oral administration of bacteriophage, as used in this study, produces no marked clinical benefit over the recognized symptomatic care and treatment.

*These studies were continued during the 1932-33 season when amounts of bacteriophage ranging from 50 to 100 c.c. were given by retention enema to each patient in addition to the bacteriophage by mouth. The treated series shows a hospitalization period of 12.3 days and the control series one of 12.5 days. These continued observations do not alter the previous conclusions.

Doctors M. F. Bigler, E. M. Kittredge, and Ruth Anderson have coöperated in this work by supervising the clinical studies. Their assistance has been greatly appreciated.

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Tuberculosis in Officers of the Regular Army*†

By Lt. Col. A. T. Cooper, M.C., *Fort Myer, Virginia*

THIS study of officers of the United States Army who have been under treatment for pulmonary tuberculosis at Fitzsimons General Hospital since January 1923 was undertaken in order to assist in arriving at an opinion of the results obtained by treatment of pulmonary tuberculosis in officers on the active list of the United States Army. All too frequently it is the usual opinion throughout the Army that when any officer contracts tuberculosis his days of usefulness for the Army are to a large extent over. Those of us who have been following the officers unfortunate enough to develop chronic pulmonary tuberculosis during their service in the Army have always realized that a large percentage of such officers can be cured and after a suitable period of time return for many years of useful service in the Army.

It is noteworthy that while this group of patients is not large, their progress and disposition have been closely followed over a number of years, as no matter where an officer may be stationed, if clinical pulmonary tuberculosis becomes evident, he is sent to the Fitzsimons General Hospital.

It has been the belief of the Medical Service at Fitzsimons General Hospital that a large percentage of officers who developed tuberculosis could, after a period of definitive treatment, be returned for active duty to the service. The records of all officers of the Regular Army on active duty who have been admitted to Fitzsimons General Hospital because of chronic pulmonary tuberculosis since January 1, 1923 have been studied. The total number was 102. It was rather a surprise to the investigator to find that the number of officers treated for pulmonary tuberculosis during a period of slightly over eight years was so small.

The following is a table showing the number of officers according to the branch of service and according to grade who have been admitted since 1923 for pulmonary tuberculosis. (See Table I).

It is seen that the junior officers, Captain, 1st Lieutenant, and 2nd Lieutenant, furnish the majority of admissions. Table 2 shows that a higher average percentage incidence of the disease occurs in these grades.

Calculating the percentage of officers admitted from each branch of the service, as is shown in table 3, gives some rather interesting information. It is seen that the Medical Corps stands out with a very much higher percentage of admissions than any

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†From the Medical Service, Fitzsimons General Hospital, Denver, Colorado.

TABLE I
Officer Patients

Branch of Service	Total Number	Grade					
		Col.	Lt. Colonel	Major	Captain	1st Lt.	2nd Lt.
Infantry	27			1	12	8	6
Engineers	4			1	1	2	
Quartermaster Corps	6		1		1	4	
Field Artillery	14			1	5	6	2
Coast Artillery Corps	11			2	4	4	1
Cavalry	6	1	1		2	2	
Air Corps	14			2	1	8	3
Medical Corps	14	1	3	3	7		
Dental Corps	2			1	1		
Veterinary Corps	1			1			
Judge Advocate General's Department	1			1			
Chaplain	1				1		
Signal Corps	1				1		
Total	102	2	5	13	36	34	12

TABLE II

	Strength in Army	Admitted to F.G.H. with pul. tbc.	Percentage
Colonels	485	2	.004
Lieutenant Colonels	593	5	.008
Majors	1898	13	.0068
Captains	3710	36	.0097
1st Lieutenants	2863	34	.012
2nd Lieutenants	1805	12	.0066

TABLE III
Percentage of Officers from Each Branch of Service

Branch	Strength	Pul. Tbc.	Percentage
Infantry	4200	27	.0064
Engineers	600	4	.0066
Quartermaster Corps	1054	6	.0057
Field Artillery	1900	14	.0074
Coast Artillery Corps	1200	11	.0092
Cavalry	950	6	.0063
Air Corps	1518	14	.0092
Medical Corps	983	14	.0142
Dental Corps	158	2	.0126
Veterinary Corps	126	1	.0079
Judge Advocate General's Department	115	1	.0087
Chaplain	125	1	.008
Signal Corps	300	1	.0033

other branch of the service, with the Dental Corps a close second. No comment is made on the possible reasons why Medical Corps and Dental Corps officers should be more prone to develop chronic pulmonary tuberculosis than officers in other branches. However, the data as obtained are herewith

recorded. It certainly appears from this that those who practise the healing arts, for some reason or other develop clinical pulmonary tuberculosis more frequently than officers in the other branches of the Army.

Table 4 shows where these 102 officers were taken ill, that is, where they first developed symptoms of clinical pulmonary tuberculosis.

end of hospitalization and the officers are then sent to protected duty. Such duty usually consists of ordinary post duties but is limited to stations in the southwestern portion of the United States, including Colorado and Wyoming, with definite recommendations that such officers not be sent on foreign service. Authorities at this hospital base these recommendations on the

TABLE IV
Where Taken Sick

United States	Hawaii	Philippine Islands	China	Panama	Alaska	Total
71	10	14	2	5	None	102

Table 5 shows the number of officers admitted each year since 1923 and the disposition of officers for each year, together with the average length of time in the hospital. Yearly admissions since 1923 have not varied greatly but since 1928 there has been a definite decrease in the number retired. This is due to the policy of retaining the officers longer under treatment in hospital. Sick-leave for two or three months is usually recommended at the

opinion that climate has therapeutic value in tuberculosis. The influence of climate may not be great but even a minimal definite benefit should be prescribed for the patient with this disease.

The first disposition of officers, showing the age and number in each grade, is given in table 6. This shows the first disposition of all officers admitted and includes in the list twenty officers who were readmitted later.

Of 102 officers who were admitted

TABLE V
Dispositions

Year	Number	Duty	Retired	Died	Transferred	Still in hospital	Average length of time in hospital		
							Years	Months	Days
1923	16	11	3	2			1	1	0
1924	11	2	6	2	1		1	2	29
1925	8	6	2				1	0	9
1926	13	5	7	1			1	1	23
1927	11	5	6				1	6	27
1928	11	3	5	3			1	6	4
1929	8	6		1		1	–	–	–
1930	15	4		1		10	–	–	–
1931 (to Sept. 1)	9	2				7	–	–	–
Total	102	44	29	10	1	18			
				Average length of time for first six years			1	3	5

TABLE VI
First Disposition of Cases

Rank	Total No.	Average age, Yrs.	Duty	Retired	Died	Still in hospital	Transferred
Colonel	2	54	0	0	0	1	1
Lt. Col.	5	48	5				
Major	13	39	9	3	0	1	
Captain	36	36	17	7	6	6	
1st Lieut.	34	32	11	14	3	6	
2nd Lieut.	12	26	2	5	1	4	
Total	102		44	29	10	18	1

to Fitzsimons General Hospital, forty-four were at their initial disposition returned to duty, this being approximately 43 per cent.

It is to be expected, of course, that a certain number of officers who are returned to duty with chronic pulmonary tuberculosis will have relapses, and table 7 shows that of the forty-four officers who, having been hospitalized for tuberculosis, were returned to duty, twenty were readmitted to Fitzsimons General Hospital because of reactivation of their pulmonary lesions. Eleven of these twenty were again returned to duty, so that of the original 102 officers, thirty-four are now on active duty. Table 7 shows the number of officers by grades who were readmitted and their disposition. Twenty-four of the forty-four officers are still on active duty and have never been returned to the hospital as patients.

The present condition of the thirty-three officers who have been retired to September 1, 1931, as to whether living or dead, is shown in table 8.

TABLE VIII

Rank	Number	Living	Dead
Colonel	0		
Lt. Col.	0		
Major	4	3	1
Captain	8	8	
1st Lieut.	16	12	4
2nd Lieut.	5	4	1
Total	33	27	6

This table (8) shows that the majority, 81.9 per cent, of these officers are still living and that 18.1 per cent died.

Table 9 shows the final disposition of all cases of pulmonary tuberculosis up to September 1, 1931 as to whether they have been returned to, and remained on duty, whether they were eventually retired, or whether they died. These are the final figures that

TABLE VII
Disposition of Active Duty Officers Readmitted to the Hospital for Pulmonary Tuberculosis

Rank	Number	Duty	Retired	Died	Still in hospital	Transferred
Colonel	0					
Lt. Col.	3	1			1	1
Major	4	3	1			
Captain	7	4	1		2	
1st Lieut.	6	3	2		1	
2nd Lieut.	0					
Total	20	11	4	0	4	1

can be calculated to September 1st and show that thirty-four, or 33.33 per cent, have been returned to duty and have remained on duty; twenty-eight, or 27.45 per cent, have been retired; seventeen, or 16.66 per cent, have died. This includes all officers who died on active duty and who died after being retired.

showed both a cavity and, at some time or other, a hemorrhage. Fifty-three, or 51.96 per cent, had cavities but no record of hemorrhage, and five had a hemorrhage without demonstrable cavity.

The disposition of the officers having these complications is shown in table 11. Fifty per cent of those hav-

TABLE IX
Final Disposition of Officers

Rank	Number	Remained on duty	Eventually retired	Died	Still in hospital	Transferred
Colonel	2				1	1
Lt. Col.	5	2	1	1	1	
Major	13	8	3	1	1	
Captain	36	14	8	6	8	
1st Lieut.	34	8	12	7	7	
2nd Lieut.	12	2	4	2	4	
Total	102	34	28	17	22	1

Those of us at Fitzsimons General Hospital who have followed the progress of chronic pulmonary tuberculosis in individual cases have realized that cavities and hemorrhages are serious complications and that unless hemorrhages are controlled and cavities are obliterated by some form of collapse therapy, the prognosis in the case is rather grave as to ultimate recovery.

Table 10 shows that fifteen, or 14.7 per cent, of these officers had hemorrhages, and that 61.76 per cent showed cavities; but only 9.8 per cent

ing cavity with a hemorrhage have either died or been retired, three are still in the hospital and only two have been returned to duty. Forty-nine per cent of the officers having a cavity without a hemorrhage have either been retired or died, and 28.3 per cent have been sent to duty. Eleven, or 20.75 per cent, are still in the hospital. This bears out the clinical observation that cavity and hemorrhage are two very serious complications. Of those that had a hemorrhage without any demonstrable cavity, four were returned to

TABLE X
Hemorrhages and Cavities

Age	Hemorrhages		Cavities		Cav. & Hem.	Cav. without Hem.	Hem. without Cav.
	No	Yes	No	Yes			
20-30	18	6	5	19	4	15	2
30-40	48	8	21	35	5	30	3
40-50	15	1	10	6	1	5	
50-60	6	0	3	3		3	
Total	87	15	39	63	10	53	5

duty, one is still in the hospital, and of those who had clinical pulmonary tuberculosis without the occurrence of hemorrhage and without evidence of cavity, 67.65 per cent were returned to duty, 20.59 per cent were retired, and 2.95 per cent died, while 8.82 per cent are still in the hospital.

in this latter table only 28.07 per cent of those showing a positive sputum were returned to duty, 33.33 per cent were retired and 15.79 per cent died, while of those who had negative sputum, 62.22 per cent were returned to duty, 22.22 per cent retired, and 2.22 per cent died.

TABLE XI
Disposition

	Number	Duty	Retired	Died	Transferred	Still in hospital
Cavity and hemorrhage....	10	2	3	2		3
Cavity without hemorrhage.	53	15	19	7	1	11
Hemorrhage without cavity.	5	4				1
No cavity or hemorrhage...	34	23	7	1		3
Total	102	44	29	10	1	18

Table 12 shows the number of officers who had positive sputum and those who had negative sputum. The largest per cent of positive sputa was found in the earlier age periods.

TABLE XII
Sputum

Ages	Number	Positive	Negative
20-30	25	20	5
30-40	55	28	27
40-50	16	7	9
50-60	6	2	4
Total	102	57	45

The disposition of these officers divided into groups on the basis of positive or negative sputum is shown in table 13. It is to be noted that

Table 14 shows the cases grouped in accordance with the types of treatment employed; and table 15 shows the disposition of the groups treated by various measures. The great majority of these patients, 81.37 per cent, either did not require any other therapy than hygienic and rest treatment, or their tuberculosis was so distributed that other therapeutic measures were not feasible.

Table 15 is of interest because it shows that of three cases on which thoracoplasty was done, two were returned to duty. Such a result should be encouraging to those officers upon whom it is necessary to do a surgical collapse. The two officers returned to

TABLE XIII
Disposition

	Number	Duty	Retired	Died	Transferred	Still in hospital
Sputum positive	57	16	19	9	1	12
Sputum negative	45	28	10	1		6
Total	102	44	29	10	1	18

TABLE XIV

Year	Total	Rest & Hygiene	Pneumo-thorax	Thoraco-plasty	Phrenic Exeresis	Phrenic Ex. & Thoraco.	Pneumo. & Phrenic Exeresis	Pneumo. & Thoraco.	Pneumo., Phrenic Ex. & Thoraco.
1923	16	15	1						
1924	11	9	1						1
1925	8	8							
1926	13	13							
1927	11	7	2	1			1		
1928	11	7	2	1		1			
1929	8	5	2	1					
1930	15	13	1		1				
1931 (to Sept. 1)	9	6	1				2		
Total	102	83	10	3	1	1	3		1

TABLE XV
Disposition

	Number	Duty	Retired	Died	Trans-ferred	Still in hospital
Rest and hygiene	83	41	23	7	1	11
Pneumothorax	10	1	3	2		4
Phrenic Exeresis	1					1
Thoracoplasty	3	2	1			
Phrenic Exeresis and Pneumothorax	3		1			2
Thoracoplasty and Pneumothorax						
Thoracoplasty and Phrenic Exeresis	1			1		
Pneumothorax, Phrenic Exeresis and Thoracoplasty.	1		1			
Total	102	44	29	10	1	18

duty are now on protected duty and one of them, at least, is making a very definite and outstanding recovery, so that there is very little doubt but that at the end of two years he can be marked apparently cured.

Rocky Mountain Spotted Fever*

By G. Gill Richards, M.D., *Salt Lake City, Utah*

ROCKY Mountain spotted fever may be described as an acute tick-born infectious disease. It was formerly thought to be indigenous to the West where it is most prevalent in the states of Idaho, Oregon, Wyoming, and Montana, but recently cases have been reported from the Atlantic states by Badger, Dyer and Rumreich[1] of the United States Public Health Service. These cases, of which there were forty in Maryland alone in 1931, are clinically and immunologically identical with those seen in the West.

The disease probably existed in the Rocky Mountain region for years before the coming of the white man. Indians feared certain valleys in the late spring and early summer because they felt that these districts were visited by evil spirits and that it was dangerous to enter them during these seasons. Cases of Rocky Mountain spotted fever were discovered in Colorado as early as 1885 but the first medical report was sent to Washington in 1896 by M. W. Wood,[2] an army surgeon, who collected data from several Idaho physicians treating these cases.

In 1899 Dr. E. E. Maxey,[3] of Boise, Idaho, published his description of this disease as a distinctly new entity.

In 1902 G. T. McCullough[4] described a type of the disease in the Bitter Root Valley of Montana which was much more virulent than that seen in Idaho.

In the same year, at the solicitation of the Montana State Board of Health, L. B. Wilson and W. M. Chowning,[5] of the University of Minnesota, made an investigation as to the nature, cause, and possible means of prevention of this disease. They described an hematozoa which they found in the blood corpuscles of patients and of gophers. They concluded that the disease was transmitted to man by the wood-tick which had become infected from certain rodents. They did not, however, offer sufficient experimental proof of this claim to lead to its general acceptance.

In 1903 J. F. Anderson,[6] of the United States Public Health Service, studied and classified the ticks of the mountain region. Stiles named the tick, which has been shown to be the chief vector of spotted fever, *Dermacentor andersonii*.

It remained for Howard Taylor Ricketts,[7] who later sacrificed his life in the interest of medical science, to establish through his painstaking scientific labors the methods by which the relationship of the tick to the disease could be demonstrated. He was able to produce the disease in laboratory

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animals by means of the tick. He demonstrated the infected tick in nature and the hereditary passage of the virus from one generation of ticks to the next. He also described a micro-organism whose etiological relationship to the disease was fully demonstrated by Wolbach in 1919.

In 1908 Dr. L. P. McCalla[8] reported the transmission of the disease from man to man by means of a tick taken from a patient's body and allowed to feed on two volunteers who contracted the disease in four and nine days respectively.

In 1916 L. D. Fricks[9] described protozoan-like bodies in the red blood cells of patients but hesitated to draw any conclusions as to their etiological significance.

In 1919 Wolbach[10] described micro-organisms which he found in the blood of many laboratory animals and in tissues of ticks infected with Rocky Mountain spotted fever. He named them *Dermacentroxenus rickettsi.*

Noguchi,[11] who like Ricketts was later to die in a foreign country of the disease which he was investigating, made many studies of Rocky Mountain spotted fever. He was chiefly interested in attempts to cultivate the microörganism and in the study of immunological reactions. In 1923 he prepared a sero-vaccine which protected the guinea pig against the disease but did not effectively protect the monkey or man.

From 1922 to 1928 R. R. Spencer and R. R. Parker[12] carried on an intensive joint research. Their studies have added many important points to our knowledge of the life cycle of the tick and the maintenance of the virus in nature. The virus has been shown to exist in an avirulent phase in the fasting tick and to become infective again shortly after the tick has fed. The ability of tick virus to pass through the intact skin has been proved, thus demonstrating how the disease may be acquired without tick bite if infective ticks are crushed in the fingers. The rôle played by other ticks than the *Dermacentor andersonii* in the transmission of the disease from animal to animal has been studied and it has been shown that at least two other species of ticks may be carriers of Rocky Mountain spotted fever virus. To Spencer and Parker is due also the successful development of a vaccine now issued by the laboratory at Hamilton, Montana and shown by several years' experience to be of great prophylactic value.

Seasonal Incidence

Rocky Mountain spotted fever has occurred in all months of the year but winter cases are very rare. Generally it is most prevalent in the spring from March to June and corresponds to the seasonal abundance of the wood tick. In the higher altitudes it often occurs in the later summer months.

The disease occurs most frequently in those people whose occupation or pleasures necessitates their presence in infected areas in the season of the year when it is most prevalent. Its incidence is therefore more common in men than in women. Children withstand the infection much better than adults. In the regions of high mortality unvaccinated adults past middle life seldom recover.

Incubation Period

In man the incubation period is from two to twelve days. Its average duration is from four to seven days. The more virulent the infection the shorter the incubation period. It is also dependent upon the length of feeding time of the infected tick prior to the bite.

Symptoms

Usually the engorged tick can be found still feeding on the patient at the time of the first examination. No lesion develops at the site of the bite, nor is there, as a rule, any enlargement of the regional lymph glands such as is seen in tularemia.

During the prodromal stage of one or two days the patient complains of listlessness, some aches and pains, loss of appetite, chilly sensations, and slight fever. These symptoms progress into a real chill, followed by high fever up to 104 and 105 degrees which lasts fourteen to twenty-one days, with morning remissions, and falls by slow lysis. The pains become general and severe, especially in the back and legs, resembling an early stage of acute articular rheumatism. The calves of the legs become very sensitive and painful to touch or movement. Hyperesthesia of the skin is often very troublesome. Nose bleed occasionally occurs. There is often a slight dry and irritating cough. The conjunctivae are often injected and sometimes hemorrhagic with accompanying photophobia. Gastrointestinal symptoms are not as a rule marked or common. As the disease progresses, the patient usually becomes increasingly anxious and restless. During the height of the fever he is often delirious.

The rash is the most constant and characteristic single sign in the course of the disease. A few patients may, however, die before the appearance of the eruption. The rash is first seen on the wrists, forearms, and ankles, usually appearing on the third or fourth day and gradually spreading to the rest of the body. It begins as a discrete, rose colored, macular eruption which at first disappears under pressure. Later it becomes blotchy and petechial in character. If the rash remains discrete and pinkish it is a favorable prognostic sign. Large spots are more favorable than small ones. The more severe types progress to a darker color, the lesions coalesce and may develop into hemorrhagic and necrotic spots. The life cycle of any given group of spots is about fourteen days, with a gradual change of the lesions to brownish pigmented areas before they entirely disappear. In the more severe types the eruption occurs in the throat and may result in some sloughing. In some cases the rash appears in one, two, or even three crops, each crop running its separate course.

The pulse is often a valuable guide to the condition of the patient. Early in the disease it is slow in proportion to the temperature, and in the milder types it often does not exceed 90 per minute. As the toxemia progresses in the severe forms the pulse becomes increasingly rapid and poor in quality. A rapid pulse is a very unfavorable sign.

Urinary changes are not common except in the older patients who often develop a suppression and die of uremia.

The blood picture is not characteristic. There is a moderate leukocytosis in the first week, increasing up to 15,000 and 18,000 in the second week with a relative increase in large mononuclear cells. Icterus is often a terminal sign in the fatal cases.

Differential Diagnosis

The disease must be differentiated from typhoid fever, cerebrospinal meningitis, especially the septicemic type, measles, typhus, and even smallpox.

In an area known to be infected the history of tick bite or, as often occurs, the finding of a tick on the patient's body, may lead to an early and an easy diagnosis.

The Weil-Felix reaction has been found to be present in the majority of cases of Rocky Mountain spotted fever, but this does not differentiate it from certain other diseases due to rickettsiae. Immunity tests may be necessary to differentiate it from typhus. Animals which have recovered from typhus are still susceptible to Rocky Mountain spotted fever and those recovering from spotted fever are susceptible to typhus but not to another inoculation of spotted fever virus.

Generally one attack of Rocky Mountain spotted fever produces a permanent immunity against subsequent exposures. There have been a few authentic reports of second attacks.

Pathology

The gross pathology is not distinctive. The subcutaneous hemorrhages and enlargement of the spleen are the only constant and striking macroscopic lesions. The lymph glands are enlarged in some cases.

Microscopically there is a perivascular infiltration of the subcutaneous tissue and the small blood vessels may be completely occluded with mononuclear cells. In the endothelial and smooth muscle cells of the media, large numbers of the minute rickettsiae bodies were first described by Wolbach and have subsequently been confirmed by others. Wolbach[10] considers spotted fever as a disease of the peripheral blood vessels or an acute endangeitis.

Complications and Mortality

Sloughing of the soft parts in the mouth or of the scrotum occasionally occurs with secondary infections. Phlebitis is not an infrequent complication. A persistent neuritis lasting for many months was very troublesome in one of my cases. Broncho-pneumonia may develop and be the cause of death. Suppression of urine resulting in uremia is seen in the older patients.

The mortality rate varies greatly in different sections and in different years, ranging from 4 and 5 per cent in the Snake River Valley in Idaho to as high as 90 per cent in some seasons in the Bitter Root Valley in Montana. Death probably occurs from a severe toxemia, which seems to affect chiefly the heart muscle and peripheral blood vessels.

Treatment

General treatment should consist of complete rest in bed in order to conserve all possible strength. The patient should be kept as quiet as possible physically and mentally by any safe

measures such as baths, packs, and the use of barbital, phenobarbital, or chloral and bromides, or even morphine if necessary. Cardiac stimulants such as caffein and digitalis should be given if there is any indication of impending cardiac failure. The intake of fluids and nourishment must be maintained as in any acute fever. If there be nausea and vomiting, as occasionally occurs, fluids may be given by bowel, or subcutaneously.

Specific Therapy

Up to the present time there is no specific drug or antiserum. Convalescent serum and transfusions from convalescent patients have been tried without benefit.

The avoidance of known infected areas during the tick season is the most important prophylactic measure. When of necessity such areas are visited it is important to search the body several times a day for ticks, since their prompt removal in the first hours after attachment may obviate infection. The use of the vaccine as a prophylactic is advised for all whose occupation subjects them to exposure.

The author wishes to acknowledge his indebtedness to Dr. R. R. Parker of Hamilton, Montana for assistance in the preparation of this paper.

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The Biological and Clinical Importance of Ovary-Stimulating Hormones*†

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ALTHOUGH it has been recognized for over a quarter of a century that a definite interrelationship exists between the anterior hypophysis and the gonads, it is only within recent years that it has been possible to study the action of substances which definitely produce anatomical effects in the ovaries. This has been due mainly to the pioneer work of Evans and Long with alkaline extracts of the anterior lobe, and to the experiments of Smith and Engle and Aschheim and Zondek with gland implants in immature animals. These findings have afforded the basis for fundamental biological tests and have led to a vast number of laboratory and clinical investigations. The object of the present paper is to present a brief summary of the more important known facts regarding "ovary-stimulating substances" and at the same time to indicate the trend of modern research in attempting to solve some of the perplexing mysteries of the "female sex hormones".

*Read before the American College of Physicians April 5, 1932, San Francisco, California.

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Definition and Biological Tests

The "ovary-stimulating substances" which form the subject of this paper may best be described by a brief reference to the biological effects that they produce, which form the basis of the laboratory tests employed for their recognition, namely, (1) the stimulation of graafian follicle development with the consequent elaboration of the ovarian hormone "estrin", (2) corpus luteum formation with the production of its hormone "progestin", and (3) ovulation or follicle rupture.

The first of these effects, follicle ripening, is demonstrated in the immature rat or mouse ovary by means of the Aschheim-Zondek test, and is commonly referred to as "Anterior Pituitary Reaction I", abbreviated to APR I. In addition to the growth of the follicle, however, it is very important to remember that there is also a resultant elaboration of the ovarian hormone "estrin", which manifests itself by a number of important changes. The vaginal outlet of the immature mouse or rat, which is normally closed by a thin membrane, swells and opens, the vaginal mucosa develops from a low cuboidal type of epithelium to a thick, cornified, squamous epithelium, and the cornua of the uterus become markedly hypertrophied.

The second change which may be produced in the immature rat or mouse ovary is an extensive luteinization, a development of granulosa cells into corpus luteum cells. This change is so intense that follicles may become completely transformed into lutein-cell bodies before ovulation has occurred and so produce the histologic picture of "imprisoned ova", the "Anterior Pituitary Reaction III" (APR III) of Aschheim and Zondek. As in the first experiment, this anatomical effect is also accompanied by the production of a hormone, "progestin", the hormone of the corpus luteum. This likewise results in the opening of the immature vagina, but the mucosa is now not cornified but composed of high cylindrical cells secreting mucus (mucification), while the uterus has acquired the property of responding to an abnormal stimulus and developing a placentoma or deciduoma. The animal, in other words, is in a state of "pseudopregnancy".

In some instances of rats or mice yielding an APR I, it may be possible by delaying sacrificing the animal for a period of twenty-four hours, to demonstrate a rupture of the fully-developed graafian follicle and the presence of ova in the cornua of the uterus. This was very well shown by Smith and Engle[1] with implants of the anterior lobe when they produced a "superovulation" in immature mice. The production of ovulation, however, is more readily demonstrated by the use of rabbits as recommended originally by Friedman.[2] The ovary of this animal normally contains fully-developed graafian follicles which may be seen grossly as small clear cysts near the surface of the organ. Following the administration of an "ovary-stimulating substance", such as is found in the urine of pregnant women, a very radical change occurs. The cysts rupture and this process is accompanied by a local hemorrhage, so that within thirty-six hours small, red, protruding areas may readily be seen grossly in the ovaries.*

It is thus apparent that the main function of the "ovary-stimulating substances" is in determining the growth, maturity, and rupture of the graafian follicle, as well as its subsequent development into a corpus luteum. Associated with these anatomical changes there is the elaboration of two ovarian hormones, (1) estrin, which in the human produces a growth of the endometrium, pelvic hyperemia, and turgor of the uterus, and (2) progestin, which is responsible for the secretory changes found in the pregravid phase of the endometrium (figure 1). This hormone (or hormones)† also seems to have a definite influence on lactation (Grüter and Stricker,[3] Corner,[4] Evans and Simpson[5]), and although not entering into the scope of this review it must be remembered that it has an influence on the male sexual organs and so is, more prop-

*In this connection attention must be directed to the presence of hemorrhage into graafian follicles or luteinized cysts which may also be found in rats or mice, and which Aschheim and Zondek refer to as APR II in their "pregnancy test".

†More recent studies by Riddle and his co-workers (Proc. Soc. Exper. Biol. and Med., 1932, xxix, 1211) suggests that there is a separate hormone of the anterior hypophysis, which they call *prolactin*, concerned with lactation.

erly speaking, a "gonad-stimulating" principle rather than merely "ovary-stimulating".

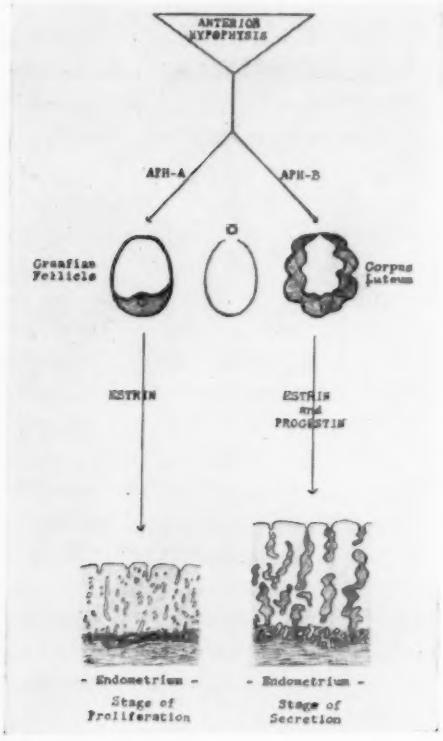

FIG. 1. Diagram illustrating the action of the anterior pituitary ovary-stimulating hormone on the ovaries, with the consequent production of *estrin* and *progestin*.

IS THERE MORE THAN ONE OVARY-STIMULATING HORMONE?

It has been shown that three very definite effects may be assigned to "ovary-stimulating substances", namely, follicle development, ovulation, and corpus luteum formation. The question immediately arises as to whether we are dealing with only one hormone which provokes these reactions in the ovaries, or whether these reactions are due to two or more hormones each of which has a specific function.

The possibility that there may be two distinct ovary-stimulating hormones was first brought out by an apparent contradiction in the work of Evans and Long, and Smith. The former workers found that the ovarian response of rats to their growth hormone extracts consisted of a delay in the appearance of estrus in immature animals with the formation of abnormal lutein bodies in the ovaries; whereas Smith, and Smith and Engle found that direct implants of the anterior hypophysis produced an early appearance of estrus accompanied by a premature development of normal follicles. In addition, it was found that the administration of Evans' luteinizing hormone inhibited the effect of implants, thus suggesting that not only were two sex hormones concerned but that they were directly antagonistic in their action (Evans and Simpson[6]). The conception of a dual hormone was also advanced by Bellerby,[7] and later Aschheim[8] supported this theory on the basis of his findings in numerous biological tests. Since then, most writers on the subject, chiefly in Germany, have assumed the existence of two ovary-stimulating hormones—one termed anteriorpituitary hormone (APH-A), stimulating growth of follicles, and a second (APH-B) responsible for luteinization (Zondek[9]). Further evidence in favor of this theory has been advanced in a number of articles (Crew and Wiesner,[10] Evans and Simpson,[11] Loeb[12]), and Fevold, Hisaw, and Leonard[13] have reported a method of extracting and separating two gonad-stimulating hor-

mones from anterior lobe tissue. They have found that one of these stimulates follicular growth while the second causes luteinization, and it is of especial interest that the luteinizing hormone they have isolated does not act on the immature ovary unless it has previously been stimulated to follicular activity by the first extract.

There is thus some evidence that there exists more than one ovary-stimulating substance, but on the other hand this conception is not widely accepted as having received sufficient experimental corroboration. It is not generally held that a chemical separation of more than one substance has been clearly accomplished (Dodds[14]), and it is possible that the different effects may be due simply to variations in dosage and methods of administration. In a recent extensive report Wallen-Lawrence and van Dyke[15] state that they encountered no evidence of two principles, and further work by Smith and White[16] indicates that under physiological conditions follicular growth and luteinization cannot be explained by the successive secretion of two hormones.

Distribution

The development of simple biological tests for the ovary-stimulating substances has resulted in an extensive search for their presence in various organs and body fluids, so that an amazing number of reports are now available on this phase of the subject. In order to simplify an analysis of these findings in the human it would seem advisable to consider them under three separate headings, namely, their occurrence (a) in normal individuals, (b) during pregnancy, and (c) in pathological conditions.

A. *Normal.* Of primary importance in this work are the findings resulting from the direct examination of the human anterior hypophysis, and it may be stated that both APH-A and APH-B effects have been obtained from the anterior lobes of men and women of all ages and even during intrauterine life (Zondek,[9] Schultze-Rhonhof and Niedenthal,[17] Siegmund and Mahnert,[18] and others). The same finding applies to animals, as for instance, cattle, sheep, pigs, rats, cats, rabbits and so forth. These observations are of great importance in view of the prevailing conception that the anterior lobe is the main, if not the only, source of the gonad-stimulating hormones.

There is as yet but little known regarding the occurrence of gonad-stimulating hormones in the blood or urine of normal women during adult sexual life. However, a recent study by Zondek[19] shows that by concentrating the urine it is possible to find APH-A at all stages of the menstrual cycle, although the greatest concentration is to be found during the premenstrual phase. In a preliminary communication, Frank, Goldberger and Spielman,[20] and Frank[21] announce that they have conducted similar studies with blood and have also been able to demonstrate APH-A in various individuals, although in this case the greatest concentration has been found early in the cycle, namely between the sixth and ninth days. On the other hand, Neumann and Péter[22] report that they find APH-A in the blood at a late stage of the menstrual cycle, between

the twenty-second and twenty-seventh days, so that this phase of the problem must for the present be considered as undetermined.

B. *Pregnancy.* The widespread dissemination of ovary-stimulating hormones in women during pregnancy is one of the most interesting discoveries relating to this work. The test in these cases is characterized mainly by the reaction attributed to APH-B, and forms the basis for the well-known Aschheim-Zondek pregnancy test which has now received worldwide recognition. In addition to urine (Aschheim and Zondek[23]) and blood (Fels[24]; Fluhmann[25]) positive tests have been obtained from the placenta, decidua, corpus luteum graviditatis, amniotic fluid, fetal blood, tubal mucosa (Aschheim and Zondek[23]), colostrum and milk (Heim[26]), saliva (Trancu-Rainer[27]), and the serum in blisters resulting from the application of cantharides (Heim[28]). Closely related to these findings are the strongly positive reactions from the urine of women with hydatidiform mole or chorioepithelioma (Rössler[29] and others). However, a remarkable observation was made by Philipp,[30] and corroborated by Ehrhardt and Mayes[31] and others, that the anterior hypophysis of pregnant women is practically devoid of ovary-stimulating substances. This would seem to be paradoxical; the significance of this finding will be discussed later.

C. *Pathological Conditions.* In normal individuals the demonstration of ovary-stimulating hormones is a complicated and uncertain procedure, though in pregnancy the tremendous amounts present render it a comparatively simple matter. However, there are certain endocrinological conditions which are also characterized by the presence of unduly large amounts of these substances in the blood or urine. As the result of the examination of a large series of patients, Fluhmann[32,33,34] has shown that a definite relation exists between ovarian function as determined by the history of the menstrual cycle and the finding of excessive amounts of ovary-stimulating hormones in the blood. These observations obtained from a large series of patients are listed in table 1, and it is seen that they may be grouped into four categories. The first two are characterized by negative blood tests, and include women with normal menses or with manifestations usually referred to as of "hypo-ovarian" origin, namely, irregular delayed menses, scanty periods, and amenorrhea. In the third group are women in whom there is a total absence of ovarian function, namely castrates, patients in the postclimacteric, and a certain number with prolonged periods of amenorrhea, and it is seen that a large percentage have given positive tests. These findings have received corroboration from the work of Zondek[9] and Mazer and Hoffman.[35] The fourth group also presents a number with unduly large amounts of ovary-stimulating substances in the blood and is of particular interest because it includes a type of patient with symptoms suggesting a possible primary hyperpituitary function.

Zondek[36] has drawn attention to similar findings in the urine of women at the time of the climacteric, following castration, and in genital carcinoma. His latter observation is of interest

because he has noted that just as in pregnancy the anterior hypophysis of these patients likewise contains a marked diminution in the amount of stored sex hormones (Zondek[37]). Neumann[38] has found that the urine of children up to the age of ten frequently gives a positive test for the presence of ovary-stimulating hormones.

same characteristics as those made from other sources, such as the urine of pregnant women (Zondek[9]). Although the two ovarian substances, estrin and progestin, are readily taken up by lipoid solvents such as ether and chloroform, this is not the case with the ovary-stimulating hormones which are soluble in alcohol at a concentration of 40 per cent but insoluble

TABLE I

Results of the examination of the blood serum of 266 non-pregnant women for the presence of excessive amounts of ovary-stimulating hormones.

	APR I	APR III	APR I-III	Total Positive	Negative	Total
I. NORMAL OVARIAN FUNCTION						
Regular 28-day menses	0	0	0	0	45	45
II. HYPOHORMONAL CONDITIONS						
Irregular delayed menses	1	0	0	1	29	30
Totally irregular menses	0	0	0	0	15	15
Scanty menses; reg. cycle....	0	0	0	0	16	16
Amenorrhea, short duration..	0	0	0	0	14	14
Amenorrhea, long duration...	0	0	0	0	16	16
III. AFUNCTIONAL CONDITIONS						
Operative castration:						
a. Within 3 mos. postop...	8	0	0	8	12	20
b. After 3 months.....	13	0	0	13	4	17
Radiation castration	8	0	1	9	6	15
Post-climacteric	5	1	3	9	6	15
Amenorrhea, long duration...	5	1	4	10	0	10
IV. HYPERHORMONAL CONDITIONS						
Menopause; irreg. menses ...	9	0	2	11	22	33
Polymenorrhea	5	1	1	7	13	20
	54	3	11	68	198	266

CHEMICAL PROPERTIES

Since it has not yet been possible to isolate the ovary-stimulating principles in pure form, their exact chemical constitution is as yet unknown, but a number of important properties have been determined as a result of the studies of Zondek,[9] Collip,[39] Dickens,[40] Wallen-Lawrence and van Dyke,[15] Goss and Cole,[41] and others. In the first place, no final chemical differentiation between APH-A and -B has been accomplished, and in the second, extracts made from the anterior pituitary gland have shown essentially the

in concentrations of over 70 per cent. They are also precipitated from an aqueous solution by high-grade acetone, sodium or ammonium sulfate, "colloidal iron" or tannic acid. They are readily adsorbed to charcoal, are destroyed by temperatures above 70°C., and are very sensitive to the action of acids or alkali, since Dickens[40] noted that 0.2N acid or alkali completely inactivate extracts made from the urine of pregnant women.

An exception must be made in the case of "Emmenin", an estrogenic substance which was isolated by Collip

from the human placenta and which he considers as an ovary-stimulating hormone. This extract is readily soluble in alcohol, is effective when administered orally, and although it causes the appearance of estrual changes in immature rats it only acts on the spayed adult animal in very high concentration. It is evident that this preparation does not fall into the same category as the ovary-stimulating substances under discussion, but it is important to note that Collip also obtains a second principle from the placenta which agrees fairly closely in its general properties to those described above.

Numerous extracts of high potency are now being prepared and used for biological and clinical studies. The anterior lobe has been used as the source of the ovary-stimulating substances by Evans and Long,[42] Putnam, Teel, and Benedict,[43] Räth et al,[44] Bugbee et al,[45] Reiss et al,[46] Bellerby,[47] Wallen-Lawrence and van Dyke.[15] The urine of pregnant women has yielded large amounts of the hormones and has been employed by Zondek[9] who gives the name of Prolan to the resultant extract, and by Biedl,[48] Dickens,[40] Wallen-Lawrence and van Dyke,[15] Evans et al,[49] and others. The human placenta has been employed by Crew and Wiesner,[10] and Collip,[39] and potent extracts have also been made from the blood of pregnant women (Fluhmann[50]), and of mares (Goss and Cole[41]).

Source of Ovary-Stimulating Hormones

Since the first studies on this problem were conducted with the anterior hypophysis, it was natural that this organ should be considered as the sole source of the ovary-stimulating hormones. However, their wide dissemination has led to some doubt on this question and a number of investigators believe that they may also have an extra-hypophyseal origin. This conception has been advanced by Philipp,[51] Collip,[39] Fels,[52] Motta,[53] and others, who claim that the placenta must be considered as capable of manufacturing as well as storing such hormones. The chief arguments advanced in favor of the theory for a placental origin of the ovary-stimulating hormone in the blood and urine during pregnancy may be summarized briefly as follows: (1) The placenta contains very large amounts of an ovary-stimulating substance (or substances); (2) the characteristic histologic pregnancy changes in the anterior pituitary gland of women do not appear until the fifth month of gestation, although large amounts of APH are found very early in the blood and urine; (3) the Aschheim-Zondek test is positive in cases of hydatidiform mole and chorioepithelioma, and becomes negative following the removal of the tumor growth; (4) the anterior hypophysis of pregnant women contains no demonstrable amount of sex hormone (Philipp,[30] corroborated by Ehrhardt and Mayes,[31] Zondek,[37] and others); (5) the substance Emmenin which Collip obtains from the placenta, and which he maintains should be considered as an ovary-stimulating hormone, differs from anterior hypophyseal extracts in its chemical properties and in many of its biological effects; (6) some differences in the effects of urine extracts and anterior pituitary implants have been reported, thus suggesting that

they may not be identical* (Engle,[54] Wallen-Lawrence and van Dyke,[15] Evans et al,[49] Loeb[55]); (7) the report of Hill and Parkes[56] and of Reichert et al[57,58] that urine extracts are relatively ineffective in inducing ovarian changes in hypophysectomized rabbits, dogs, and rats may be interpreted as meaning that these preparations are not hypophyseal hormones since they apparently cannot substitute for this organ.

It would seem that there is evidence in favor of an extrahypophyseal origin for ovary-stimulating hormones, but on the other hand there has been considerable opposition to accepting this theory. In the first place, the presence of the hormones in the placenta by no means necessitates their manufacture there, and it would be just as reasonable to state that ovarian cysts and the mammary and salivary glands also can produce ovary-stimulating substances since they have been found in cyst fluid (Zondek[37]), milk and colostrum (Heim[26]), and saliva (Trancu-Rainer[27]). The characteristic pregnancy changes of the anterior lobe may not be complete until the fifth month, but on the other hand the large amount of hormones in the urine appears so early in pregnancy that some doubt must be expressed as to whether the placenta has sufficiently developed at that stage to produce such quantities (Zondek[37]). The diminished amounts of ovary-stimulating substances present in the anterior lobe of pregnant women may not mean a lowered production on the part of this gland but an increase in their utilization by the body so that none remains stored up in the hypophysis (Zondek[37]). In pregnant cows and pigs there is no hormone demonstrable in the blood or urine, and since there is not the same call for large amounts of this substance as there is in the human, the anterior lobe of these animals has a normal hormone content. The experiments of Collip with Emmenin show that he is dealing with a hormone which apparently has no counterpart in the anterior lobe, and some doubt must be expressed as to whether it can strictly be included in the group of "ovary-stimulating" substances considered in this paper because it does not produce histologic changes in the ovaries of immature rats and is effective in young castrates (Collip[39]). The biological differences between anterior lobe and urine extracts is an important observation, but is not necessarily conclusive evidence that the hypophysis is not the source of the ovary-stimulating substances. Some of the variable results may be due to differences in dosage, and the preparation of the extracts may possibly cause chemical changes interfering with the normal action of the hormones. This is well illustrated by the experiments of Hill and Parkes[59] who found that they were unable to induce ovarian changes in hypophysectomized rabbits with urine extracts but could produce this effect fairly readily by the injection of untreated urine.

This question must therefore remain open for the present. It is considered proved that an ovary-stimulating hormone is manufactured by the anterior hypophysis, but the origin and the exact nature of that found in women during pregnancy is not established.

*Since this paper was written a year ago additional evidence has accumulated pointing to biological differences in the ovary-stimulating principles of the anterior hypophysis from those of blood or urine of pregnant women.

Therapy

It was only natural that as soon as active preparations of this hormone were available, attempts should be made to utilize it as a therapeutic agent. It was also to be expected that it should be applied to the treatment of functional conditions which have generally been considered as of "hypo-ovarian" origin. It is very generally appreciated that there are many difficulties associated with the care of such disturbances, due to the fact that symptoms and not diseases are treated and that there is an unknown percentage of spontaneous recoveries. In addition, the question of determining proper dosage and methods of administration is one which is as yet unsolved. However, a number of favorable reports dealing with the use of ovary-stimulating preparations in women with amenorrhea, delayed menses, and scanty menses are available (Zondek,[9] Campbell and Collip,[60] Seitz,[61] Hirsch-Hoffmann and Wulk,[62] Koehler,[63] Ehrhardt,[64] and others) and suggest that this method of approach must be thoroughly investigated. The good results from the injection of whole blood or blood serum from human pregnant donors reported by de Maortua[65] and Esch,[66] as well as Zondek's experiments with the extracts[9] suggest that a solution may be found in the combined administration of ovary-stimulating and ovarian hormones. It is also worthy of note that Zondek[9] observed a congestion of the pelvic organs and an increase of the temperature of the vagina and rectum following the use of Prolan, and recommends this procedure as part of the conservative treatment of pelvic inflammatory disease. This is of interest since it has been shown that a much more extensive response of tissue histiocytes to a local irritation can be elicited in the rabbit's uterus when a condition of pseudopregnancy has been set up by the injection of pregnancy urine (Fluhmann[67]).

The most hopeful therapeutic result reported to date, however, is the use of ovary-stimulating extracts made from pregnancy urine or placentae for the treatment of certain types of menorrhagia and metrorrhagia (Martin,[68] Campbell and Collip,[60] Novak and Hurd,[69] Siebke[70]). The large percentage of favorable results which has been obtained by this method for the control of the hemorrhages associated with hyperplasia of the endometrium is very impressive, and it would seem that we now have an effective medical treatment for these patients.

Comment

It is thus seen that the ovary-stimulating hormone (or hormones) is a very important factor in the normal physiology of the sexual organs, but it would be hazardous to attempt an exact evaluation of its rôle owing to the obscurity that yet exists as to the interrelationship of the ovaries and the anterior hypophysis. It is evident, however, that it does play a vital part, and as future work yields further information regarding the factors that control the interaction of these glands it will be possible to understand more fully many obscure features concerning puberty, menstruation, pregnancy, and lactation.

On the other hand, it cannot be denied that much progress has also

been made from a clinical standpoint. In the first place, this work has given a new diagnostic procedure, the Aschheim-Zondek test, which has received worldwide approbation and is in general usage. This test is not only highly efficient in recognizing early pregnancy but has been utilized as a control for the successful treatment of chorioepithelioma and hydatidiform mole. Secondly, a more extended use of this test has yielded an additional method of approach for the study of certain endocrinological conditions which are accompanied by disturbances of menstruation. As these investigations are carried further and coupled with studies on the ovarian hormones, there is no doubt that new light will be thrown on the etiology of various disturbances such as amenorrhea, polymenorrhea, and the menopause. And finally, some progress has been recorded from the therapeutic use of ovary-stimulating principles. The results in no way can be said to compare with the hopes and enthusiasm that their discovery initiated, but the mere fact that there is now an effective medical treatment for the uterine hemorrhage accompanying hyperplasia of the endometrium justifies all these endeavors.

Summary

The term "ovary-stimulating hormone" is used for certain biological substances which stimulate the growth of graafian follicles, ovulation, and corpus luteum formation, resulting in the production of the ovarian hormones estrin and progestin. It is believed that there are two such hormones, but the evidence is incomplete. The ovary-stimulating principles are chiefly in the anterior hypophysis, but during pregnancy in the human they are widely disseminated in the body of the mother and of the fetus. They have been demonstrated also in the blood and urine of patients with amenorrhea, following castration, and in the post-climacteric period. The evidence obtained to date favors the conception that the anterior lobe of the hypophysis is the main source of these hormones, but it has been suggested that one type may have an extra-hypophyseal origin. From a clinical standpoint, three important advantages have resulted from these studies: (1) the development of an important test for the diagnosis of pregnancy and the control of the treatment of chorioepithelioma and hydatidiform mole; (2) the employment of a new method of approach for the study of certain endocrinological conditions which are accompanied by ovarian disturbances; and (3) the use of extracts of ovary-stimulating hormones for the successful treatment of the uterine hemorrhages accompanying hyperplasia of the endometrium.

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Animal Experiments with Adrenal Cortical Extracts*†

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SINCE the extraction of a potent principle from the adrenal cortex by Swingle and Pfiffner[19] and by Hartmann[8] much greater interest has centered upon this gland than ever before. Animal experimentation has at last acquired a tool to work with, and it is being used extensively. Great hopes have been entertained for the successful treatment of Addison's disease, and the cortical extract has been used for this purpose with some degree of success by Rowntree and others.[16] The very nature of this condition, however, would preclude the possibility of a cure, since it is caused in most cases by a progressive, destructive lesion of the adrenal glands. The only hope therefore is that cortical extract can replace the normal secretion. This would mean lifelong treatment, though in rare instances of tuberculosis of the glands, it might be that treatment would be necessary only through a critical period of greatest adrenal insufficiency and could be discontinued if the disease in the glands became arrested. Examples of cured or healed tuberculosis of the adrenals, however, must be very rare.

One is reminded of the discovery of insulin, and the optimism which prevailed as to the cure of diabetes; but in spite of insulin, the mortality from this disease is greater than ever.[14] Also, the failure of Collip's parathormone to replace completely the secretion of the parathyroid glands has been reported by Lisser and Shepardson.[10] Because of these recent experiences, adrenal cortical extract has probably not excited clinicians as much as it has those working in the field of experimental biology. For the present, its biological significance far outweighs the possibility of its clinical application.

Even before a cortical extract was available, a considerable amount of knowledge had been assembled through clinical observation and pathological study, as well as by experiments upon the effects of adrenalectomy. Briefly, lesions causing hypofunction of the cortex have been associated with: (1) pseudohermaphroditism in the newborn; (2) a questionable failure of development of the central nervous system in anencephaly (probably coincidental); (3) hyperplasia of the

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thyroid[21]; (4) Addison's disease; (5) myasthenia gravis.

Lesions which cause hyperfunction of the adrenals (hyperplasia, adenomas, functionating carcinomas) are associated with, or may cause: (1) precocious puberty; (2) so-called adrenal virilism, masculinism, or a condition of pseudohermaphroditism in the adult female; less well-defined sexual changes (as gynecomastia) in the adult male. This list omits, of course, all conditions which have been attributed to malfunction of the adrenal medulla.

It is these physical and sexual changes which have interested us most. The adrenal cortex is so intimately bound up with, not only the phenomenon of reproduction, but the physical configuration of the body, that these aspects seem to be of much greater biological significance (and probably, in the future, of greater practical significance) than the more dramatic, but much more rare disease called Addison's disease. We have, therefore, confined our studies to a few of the thyroid and sexual phases now susceptible of investigation. Rats were used advisedly, despite the impression that the adrenals cannot be removed completely from these animals. Pencharz, Olmstead and Giragossintz[15] and Freed, Brownfield, and Evans[6] have shown that when a careful operation is performed, all rats die in from five to eight days. Carr, in this work, has had an average mortality of 88 per cent in less than eight days. In those rats which did not develop signs of acute insufficiency in six days, it was concluded that the operation had not been complete, and the animals discarded, unless the experiment called for animals in a state of chronic insufficiency. It is not our purpose in this paper to detail the large number of animal experiments which have been made, but rather, by citing some of the results, to point out the trend of adrenal gland investigations, and to show how these, in time, will undoubtedly clear up many clinical problems. Biological research can no more be divorced from clinical medicine than can mathematics from astronomy.

The connection between the adrenal glands and the gonads is obvious in spite of many apparent contradictions. The production of precocious puberty and the neutralization of the sex glands after puberty by hyperfunction of the adrenal cortex presents a seeming paradox. One case of masculinism reported by Gibson,[7] and seen by us, had the hirsutism and enlarged clitoris of adrenal virilism (she had a large adrenal tumor at operation), but while presenting these masculine features, she also had definite hyperplasia of the endometrium exactly similar to the decidual reaction of pregnancy. Corey and Britton[5] have reported a change in the ovaries and testes of rats following the administration of Swingle and Pfiffner's extract which they interpret as evidence of precocious puberty, and Connor[3] has reported degeneration of the ovaries of chickens following injections of a watery extract of adrenal cortex. Müller[13] likewise produced regressive changes of the sexual apparatus of rats. We were able[4] to stop the estrus cycle of mature rats by injections of watery extracts of adrenal cortex, but, using an extract prepared by us after Swingle and Pfiffner's method, we

could not confirm Corey and Britton's results as to precocious puberty. It is nevertheless obvious that at least some of the sexual changes which have been found clinically have been reproduced experimentally, and that certainly progress towards the solution of these problems may be reported.

The retrograde sexual changes in adrenal insufficiency were first noted in a series of eighty normal animals. Following the estrus cycles of mature female white rats by vaginal smear we found that the normal sexual rhythm stopped following adrenalectomy. Autopsy findings in these animals showed a consistent and early degeneration of the corpora lutea of menstruation. It was this association that led Vincent[20] to suggest that the corpora lutea acted as accessory adrenal cortices, and by this mechanism Stewart and Rogoff[18] explained the longer postoperative survival period of pregnant dogs. The corpora lutea of rats are constantly present in the rat ovary as bodies of menstruation, lactation, or pregnancy. We were able to observe the same degeneration of the corpora lutea in three biological stages, that is not only during the estrus cycle but also in the ovaries of either lactating or pregnant animals after adrenalectomy. Similarly, subsequent to the degeneration, lactation ceased and if occurring on or before the sixteenth day of gestation, pregnancy was interrupted. The corpora lutea are not essential in pregnancy after the seventeenth or eighteenth day of gestation, and although after this period the same degeneration of the corpora lutea was noted, the animals went on to term, either delivering without lactation and dying a few days after parturition or dying in labor from asthenia and uterine inertia with the young stuck in the birth canal. It would seem then that these retrograde changes in adrenal insufficiency work by a secondary mechanism through the corpora lutea which degenerate, interrupting all normal sexual processes.

With an extract made after the manner of Swingle and Pfiffner, and known, through constant assay on adrenalectomized rats to contain the viable principle described by them, we attempted to prevent this degenerative change. With this extract we were unable to do so. The corpus luteum degeneration with inhibited estrus, or lack of lactation and abortion in the pregnant animal, continued as usual. In fact the degenerative changes were more marked in several injected cases than in those animals with untreated adrenal insufficiency. In the male, loss of libido and potency were noted due to degeneration of the cells of the seminiferous tubules. Here again a cortical extract known to contain the viable principle was ineffective in maintaining potency and preventing this degenerative change. It seemed to hasten rather than to retard it.

To study Vincent's theory that the sex glands contribute a substance to augment or replace cortical secretion, the postoperative survival period of adrenalectomized animals with and without the gonads was taken. Both in males and females the animals without gonads lived longer than those with, although cortical extract would keep either class alive indefinitely.

For many years Warthin[21] insisted that Graves' disease was a constitu-

tional disease of which hyperplasia of the thyroid was only a part. He called attention to the presence also of hyperplasia of the thymus and lymphoid apparatus and hypofunction of the adrenal glands. Experimental evidence has been accumulating that part, if not all, of this anatomical complex can be produced by causing adrenal insufficiency. Jaffe[9] noted hypertrophy of the thymus in adrenalectomized animals. Marine, Manley, and Baumann[12] observed the same thing, with also hypertrophy of the thyroid. More recently Scott and Bradford[17] regularly found an enlargement of the thymus in adrenal insufficiency. We can add that animals suffering from total or partial lack of adrenal cortical secretion show definite enlargement of the thymus as well as generalized lymphoid tissue hyperplasia, and a peculiar change in the thyroid to be regarded as an hypertrophy rather than a true hyperplasia. There is a change in the staining quality of the colloid, and a prominence of the acini not found in the normal gland. A more prolonged experiment may produce more pronounced changes.

Zwemer and others have found that thyroidectomized cats live longer after adrenalectomy than normal adrenalectomized animals. If the normal adrenalectomized cats are given thyroid extract the postoperative survival period is still further shortened. We have found this mechanism operative in the rat, the animals with both adrenals and the thyroid gland removed living 35 per cent longer than adrenalectomized animals retaining the thyroid gland. If the simple adrenalectomized animal is given thyroid extract, the survival period is still further shortened. We are at present giving both thyroid and adrenal cortical extract to adrenalectomized rats to discover whether or not this antagonism, biologically suggested, exists in the chemically extracted gland substance.

These specific changes are interesting but still less important clinically than the reaction of animals with adrenal insufficiency to environment and diet. For instance, we have been able to vary the postoperative survival period of adrenalectomized animals over 100 per cent by regulations of diet alone. Certain vitamin deficiencies and a high protein diet shorten the survival period, while a high fluid intake, additions of starches and other substances, extend it. Wide daily fluctuations in temperature influence the animals badly, while a climate a degree or two above that of the body is beneficial.

We believe that the diet and other elements of general treatment are as important in maintaining the life of animals with adrenal insufficiency and of patients with Addison's disease as is the extract itself, and that while this extract does maintain life it still lacks certain components essential to a biological equilibrium.

Summary

We have shown that a definite connection exists between adrenal insufficiency and such changes in the lymphoid apparatus as regeneration or hypertrophy of the thymus and hyperplasia of the lymphoid elements.

In the thyroid an increase in size accompanies adrenal insufficiency. The

removal of the thyroid gland extends the postoperative survival period of adrenalectomized animals. Those with adrenal insufficiency are killed by a dosage of thyroid extract which does not affect the normal animals.

The reproductive system responds to adrenal insufficiency by: a cessation of estrus; a softening and atrophy of the testicles; abortion or resorption of the fetuses (if the insufficiency occurs before the seventeenth day of gestation); and cessation of lactation. All of these changes apparently operate through the secondary atrophy of the gonads.

We were unable to prevent any of these changes by administering cortical extract carrying the viable principle.

The effect of the extract in normal animals has produced a cessation of the estrus cycle of rats, and degeneration of the ovary of chickens.

Finally, cortical extracts as made by us either contain more than one principle or else we have not extracted the complete biological unit.

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Editorials

"MEDICAL CARE FOR THE AMERICAN PEOPLE"

At a meeting of the Board of Regents of the American College of Physicians on February 7, 1933, the Committee on Public Relations offered a report on the final publication of the Committee on the Costs of Medical Care, entitled "Medical Care for the American People." By a resolution, the Board of Regents approved the report of the Committee on Public Relations and directed that it be printed in the ANNALS OF INTERNAL MEDICINE.

REPORT OF THE COMMITTEE ON PUBLIC RELATIONS

The final report of the Committee on the Costs of Medical Care is entitled: "Medical Care for the American People."

It is the twenty-eighth publication of a series representing an extensive and intensive effort to collect the factual data concerning numerous problems involved. These studies were made over a period of five years, with the expenditure of an extraordinary amount of thought, effort, and money.

The facts presented are of immense importance to the country as a whole and the medical profession in particular. They deserve the most careful study and consideration.

The detailed information is contained in the twenty-seven interim reports previously published, and only a brief summary is included in the final report. The main emphasis of the final report is placed upon certain definite recommendations proposed by the Committee as the basis for a plan of reorganization of medical practice, so as to meet the social and economic defects of the existing system brought out by the factual data.

These recommendations are in the form of separate majority and minority reports with a few members of the Committee declining to assent to either report.

The widespread discussion which has followed the publication of the final report is centered upon the recommendations suggested. This is most unfortunate as it has overshadowed the great value and significance of the studies upon which these recommendations are presumably based.

It is the opinion of your Committee that the publication of definite recommendations was premature and unjustified by the facts presented. A careful analysis of the text of the reports shows that the recommendations are really only tentative suggestions for future consideration and careful experimentation, and in our opinion should have been offered as such.

It is also our belief that the actual factual data contained in the various reports are of such value that they deserve most careful study on the part of the medical profession. These facts reveal a situation which calls for con-

sideration and action leading to modification of existing medical practice, and in any such modification the medical profession should take a leading part.

It would be very unfortunate if prejudice caused by differences of opinion concerning the recommendations should belittle the value of the facts themselves. It would be still more unfortunate if either prejudice or inaction should deprive the medical profession of its rightful position of leadership in any program for remedying existing inequalities or injustices in the operation of the practice of preventive and curative medicine.

Our Committee, therefore, recommends that the individual Fellows of the American College of Physicians be urged to study the facts presented in the report of the Committee on the Costs of Medical Care, uninfluenced by the acrimonious discussion which has been raised by the publication of the various recommendations; and we also recommend that the organized representatives of the medical profession in each community be urged to consider these problems in the light of their varying local needs and conditions, for it is our belief that by this method the enlightened leadership of the medical profession can point the way to improvements of great value, both to the public and to the medical profession itself.

THE NATIONAL BOARD OF MEDICAL EXAMINERS

Examinations and the testing of knowledge have ever been an essential part of medical training. The extraordinary development of medical knowledge within the last three decades has had a bewildering effect on the entire problem, and it seems almost as if we have outrun our educational system framed in simpler days and under simpler conditions.

Osler once remarked that examinations may be the best or the worst of an education. He further stated that they can be very helpful if an integral part of the training, but have been known to be the intellectual ruin of many good men.

The multiplicity of examinations, college, hospital, and licensure, with the general lack of uniformity, emphasized the need of a central qualifying body such as the National Board of Medical Examiners. It was organized in 1915 and the first examination was held in October 1916. During the first six years the examination included written and practical tests in the six fundamental sciences and four clinical branches and lasted for a period of seven days.

In 1922 the examination was divided into three parts, the first, which is taken after the completion of two or more years of the medical school course, being a written test in the six pre-clinical sciences: anatomy, biochemistry, physiology, pathology, bacteriology, and pharmacology. The second written test includes the four clinical branches, medicine, surgery, obstetrics and gynecology, and public health, and is taken at the completion of four years of study. Part three is taken only after one year of satisfactory hospital interne service.

This examination comprises: clinical surgery, including applied anatomy, surgical pathology, and the surgical

and head specialties; clinical medicine, including neurology, pediatrics and dermatology, clinical laboratory, medical pathology and applied physiology, biochemistry, pharmacology, and roentgenology; obstetrics and gynecology, and public health (which also includes applied bacteriology).

The written tests are conducted on the proctor plan and are held in the different medical college centers in the United States and Canada. The practical and clinical part three examination is conducted at twenty centers in different sections of the country. At each of these centers a subsidiary board of examiners has been organized, under whose supervision the examination is conducted.

The membership has been gradually increased from the original fifteen members to the present membership of twenty-seven, representing the three federal medical services, the Association of American Medical Colleges, the Council on Medical Education of the American Medical Association, the Federation of State Medical Boards, and twelve members from the profession at large, selected with special reference to their geographical distribution. To prevent "life membership" and to ensure the frequent election of new members, the Constitution provides that, with the exception of the members from the Federal services, each member is elected for a term of six years and can succeed himself for one additional term only.

By continuous and intensive study a comprehensive examination has been developed in keeping with the highest medical training now prevailing in American medical schools. Successful candidates are granted a certificate as a Diplomate of the National Board, and are permitted to use the letters D.N.B. after their names. They are so designated in the Directory issued by the American Medical Association. This certificate has been recognized by forty-two states, being accepted in lieu of the required state medical licensure examination. It is also accepted as satisfying by the qualification boards of England, Scotland, and the Irish Free State for admission to the clinical part of the final examination for entry on the British registry.

The plan of examination has served as a model for state boards and has greatly promoted the more extensive use of the practical and clinical tests in licensure examinations. The national boards of examiners in the different specialties organized in recent years have patterned their examination largely after that of the National Board.

The adoption of the examination by a number of leading medical schools is a significant endorsement. Yale University Medical School requires all students to take and pass the National Board examinations; the answer papers are graded by National Board examiners. The students at Yale take an oral comprehensive examination at the end of their second and fourth years respectively, and unless successful in these oral and practical examinations, they are not eligible for the National Board examinations.

Beginning this year Duke University requires all its students to take the National Board examination. The answer papers are held for three days, examined by the Faculty for their own purposes and records, then forwarded

to the National Board's office where they are graded in the usual way. The same plan prevails at the College of Medical Evangelists, Los Angeles, where all students are required to take the National Board examination.

At the University of Minnesota the students have the choice of taking either the National Board's written examination, or the Medical College comprehensives at the end of their second and fourth years. The papers are first graded by the Medical Faculty and then forwarded to the National Board office.

Georgetown University has announced that beginning next year it will require all students to take the National Board examination. The plan is also being considered by the University Medical Schools of Iowa, Illinois, Columbia, Colorado, Buffalo, and Washington (St. Louis), as well as several of the two-year schools.

It is interesting to note that each year a considerable number of candidates are completing their National Board examinations, after having secured their medical license, which indicates that it is steadily gaining recognition as an honors examination.

By influencing the present tendencies of medical education, unifying examination procedure, and developing a comprehensive qualifying test to determine fitness to practise, the National Board is to a certain extent fulfilling its purpose and destiny.

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SPOTTED FEVER IN THE EASTERN STATES

The identification in the rural districts of the southeastern states of a form of Rocky Mountain spotted fever was reported by Rumreich, Dyer, and Badger in 1931. In several papers in the Public Health Reports of that year[1,2,3] they published the evidence on which the identification was based. A clinical study was made of fifty cases of a spotted fever occurring during the tick season in rural districts of Delaware, Maryland, Pennsylvania, Virginia, North Carolina, and the District of Columbia. These cases were compared with fifty urban cases of typical endemic typhus occurring in Baltimore, Savannah, Tampa, and in smaller urban communities in Georgia and Florida. Suggestive clinical differences were found between the two groups of cases. The rural group showed evidence of a more severe infection by greater prostration, higher fever, and a faster pulse. The rash in the typhus group appeared first on the trunk, was less marked on the forearms, and rarely involved the palms. In the rural cases, however, the rash appeared first about the wrists and ankles, usually involved the palms and soles, spread rapidly over the whole

[1]DYER, R. E., RUMREICH, A., and BADGER, L. F.: Typhus fever; a virus of the typhus type derived from fleas collected from wild rats, Pub. Health Rep., 1931, xlvi, 334-338.

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trunk, and frequently became purpuric and confluent.

Disturbances of the central nervous system of a severe order, such as meningismus, clonic twitching, and coma, were more common in the rural group. The death rate in this rural group was 14 per cent, while there were no fatalities among the fifty cases of endemic typhus. The duration of the disease in the endemic typhus group was from eleven to sixteen days, with twenty-eight of the cases terminating on the fourteenth day. Over half of the rural cases, however, persisted to between the seventeenth and the twenty-second day. It was felt by the authors that the disease in the rural group of cases did not correspond to the clinical picture of endemic typhus but resembled the spotted fever of the Rocky Mountains more closely than it did any other disease. This suggestive clinical differentiation was supported by epidemiologic data showing that in addition to the distinguishing feature of urban, as opposed to rural, residence the typhus group gave a history in thirty-nine cases of association with rats and presumably rat fleas, whereas in the rural group rodent infestation of patients' homes was determined in only seven cases. Twenty-four of these rural cases, however, gave a history of tick bite within three weeks prior to the onset, and three more of the patients had crushed engorged ticks removed from dogs. All had lived in tick-infested localities.

Blood from three cases of the rural type was injected into guinea pigs that proved susceptible, and strains of virus were perpetuated through many generations of these animals by transfers. The lesions of the disease in guinea pigs were found in general to be similar to those caused by the Rocky Mountain spotted fever virus. Guinea pigs which had recovered were found to be still susceptible to the virus of endemic typhus and of European epidemic typhus but to be unaffected by inoculation with the virus of Rocky Mountain spotted fever.

An account of the gross and microscopic pathology of the eastern type of Rocky Mountain spotted fever, based on a study of five autopsies, has been presented in an article by Lillie.[4] In general the lesions found were similar in character, if not always in degree of severity, to those described in the twenty-one reported autopsies of Rocky Mountain spotted fever. In such small series minor variations might well be expected. It would seem, however, that in the eastern type focal brain lesions of vascular degenerative, proliferative, and focal gliotic character were more frequent than in the western form of the disease. These brain lesions were apparently closely similar to those described in European typhus. Lillie mentions the finding of "cell inclusions resembling rickettsiae in the endothelia and walls of small vessels". A more definite identification of rickettsiae in the human tissues is reported by Pinkerton and Maxcy[5] in connection with their study of a fatal case which at the time was

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[5] Pinkerton, H., and Maxcy, K. F.: Pathological study of a case of endemic typhus in Virginia with demonstration of *Rickettsia*, Am. Jr. Path., 1931, vii, 95.

thought to be one of endemic typhus, but which Maxcy now believes to have been spotted fever. More recently the identification of rickettsiae in the tissues of three cases of spotted fever has been reported by Pincoffs and Shaw.[6]

The occurrence of spotted fever on the eastern coast is therefore established by clinical epidemiological, immunological, and pathological data. Our knowledge, however, of the occurrence of the virus in nature in this eastern territory is still entirely fragmentary. It has been shown that the American dog tick (*Dermacentor variabilis*), which is the most common man-biting tick in most of the known infected area, can transmit the virus from guinea pig to guinea pig and that the virus in the tick persists through at least one moult. The importance of this species of tick as a vector of the disease in the east is further established by the finding, in an infested area, of dog ticks which were proven to be infectious by animal inoculation.[7] Further extensive studies of the other eastern ticks that may be possible vectors, and of the susceptibility of eastern rodents and small mammals which may serve as hosts, will no doubt be carried out to bring our knowledge of the maintenance of the eastern virus in nature at least abreast of what is known concerning the western virus of this disease.

It cannot readily be determined whether we are witnessing the appearance of spotted fever in the east or merely its discovery. The striking clinical characteristics of the disease favor the presumption that it could not have gone unrecognized as a clinical entity for many years. The heavy tick infestation of the southeastern states and the relatively dense human population in the same area make of all this region a potentially more important focus of the disease than the sparsely settled mountain states. That there are as yet unknown factors which affect the extension of the disease is shown, however, by the well known example of the situation in the Bitter Root valley. In this region spotted fever in humans has been known on the western side of the valley for over thirty years but has not yet spread to the eastern side, though the wood tick which transmits the virus and the rodents which serve as hosts are present on both sides. Study of this disease in the east may disclose similar instances of geographic limitation.

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[6] PINCOFFS, M. C., and SHAW, C. C.: The eastern type of Rocky Mountain spotted fever; report of a case with demonstration of rickettsiae, Medical Clinics of North America, March, 1933. (In press)

[7] BADGER, L. F.: Rocky Mountain spotted fever (eastern type); virus recovered from the dog tick *Dermacentor variabilis* found in nature, Pub. Health Rep., 1932, xlvii, 2365-2369.

Reviews

Streptococci in Relation to Man in Health and Disease. By ANNA W. WILLIAMS, xi + 260 pages, with 8 plates. Williams and Wilkins Company, Baltimore, 1932. Price, $5.00.

The streptococci, among the earliest of the pathogenic bacteria to be observed, have ever since been a center of interest and a source of much discussion. Notwithstanding many investigations, our knowledge of this group was, for a time, in a state bordering on the chaotic. Although much has been done to bring some semblance of order out of this confusion, much, however, remains to be accomplished before the situation is completely clarified. The monograph of Dr. Williams makes a distinct contribution towards this needed clarification.

The book is based not only upon a wide reading of the literature but also upon original research. After a brief historical sketch there is a chapter devoted to the general characteristics of the streptococci and the use of these in the identification of these microörganisms. Attention is called to the importance of absorption of agglutinins in the determination of agglutinative types. There is a consideration of the incidence of streptococci in nature and of the hygienic implications of their distribution. This is followed by a discussion of the relationship of streptococci to local and general infections. The author notes the part played by local immunity in streptococcal infections, considers the specificity and complexity of the exotoxins secreted by hemolytic streptococci and stresses the necessity of antigenic analysis by reciprocal absorption of agglutinins in determining the relationship of strains from different diseases. The bearing which this complicated endotoxic structure of the beta streptococci his on prophylactic vaccination and serum therapy is discussed. At the end of this section a tentative classification of the hemolytic streptococci is suggested, which is based, in part, on the hypothetic complex structure of the antigen. In a final chapter the author presents in summary the knowledge gained and the inferences that may be drawn from the various studies considered in the monograph. The book is illustrated by eight plates and has a well selected bibliography. Unfortunately, there are far too many typographical errors.

From the very nature of the subject the monograph contains much controversial matter and many divergent opinions. These various points of view receive well-balanced treatment and, where it is possible, definite conclusions are reached on the basis of experimental data. All in all this should prove a valuable accession to the library of the clinician as well as of the laboratory worker.

F. W. H.

Physical Chemistry for Students of Biology and Medicine. By DAVID I. HITCHCOCK, Ph.D., Associate Professor of Physiology in the Yale University School of Medicine, Ed. I, xi + 182 pages, 14 x 23 cm. Charles C. Thomas, Springfield, Ill., 1932. Price, $2.75.

Recognizing the importance of physical chemistry as a basis for the explanation of fundamental physiological phenomena, the author has written this volume specifically to fulfill this requirement. In no sense is this book to be considered an exhaustive treatise on physical chemistry, and perhaps its general usefulness will be materially augmented by the policy of the author in confining his discussion to the applications of physical chemistry to physiology.

The book contains elementary treatments of such subjects as the gas laws, solutions and hydrogen-ion concentration, colloids, membrane equilibria, equilibria in blood and energy transformations. Other topics of lesser importance to physiology are discussed also.

In the closing paragraphs of most of the chapters the author includes an excellent summary of the application of the specific physicochemical phenomena to physiology. It is regretted that this has been omitted in the chapter on colloids where the applications are numerous and basically important.

Of special interest is the fact that the

more modern concepts of the dissociation of strong electrolytes as set forth by Debye and Hückel are included.

It is unfortunate that on page 51 and subsequently the author uses parentheses to indicate ion concentrations. This is confusing, as the comprehensive treatises on the subject employ brackets to indicate concentration and parentheses to connote ion activity. The reviewer is of the opinion that an elementary discussion of activity coefficients and ionic strength of solutions in their relationship to the colorimetric determination of pH would enhance the value of that specific chapter.

The chapters on "Equilibria in Blood" and "Reaction Velocity and Enzyme Action" are particularly clear in expression and comprehensive. The fundamental researches of Van Slyke and others in this field are presented in a manner which should not be difficult for the student to comprehend, as much of the mathematics involved has been dispensed with.

The volume fulfills the purpose for which it is intended. The reviewer believes that it, in addition to serving as a student's textbook, will be profitable to teachers of most of the clinical courses in medical schools.

J. C. K., Jr.

Colonic Irrigation. By W. Kerr Russell, M.D., B.S., Medical Officer-in-Charge, Light and Electrical Departments, Miller General Hospital for South East London; Co-Director, Almeric Paget School of Physiotherapy, Miller Hospital. ix + 191 pages, 28 figures. William Wood & Company, Baltimore, 1932. Price, $3.00.

This is a timely book, for it comes when the approval of the Council on Physical Therapy of the American Medical Association is being sought for a deluge of colonic irrigation devices. The book is remarkably complete for its size. Although the author quotes some of the literature in which there is doubt as to the efficacy of colonic irrigation, it is evident that he deems it a most valuable therapeutic measure when properly used.

A chapter is devoted to colonic lavage apparatus. Some of these are so elaborate that they doubtless carry with them a psychotherapy far more effectual than any of the usual measures employed. Mention is hardly made of the simple one- and two-tube irrigating arrangements so frequently used in this country. The chapter devoted to different methods of administering colonic irrigation discusses each method in detail. There is said to be no object in having the colonic catheter more than two to three inches long, especially as it has been proved that fluid injected into the rectum generally reaches the cecum in about ten minutes. However, the author speaks of the introduction of catheters into the cecum. Such a procedure seems irrational, to say the least. The physiological effects of colonic lavage are fully discussed. Considerable space is allotted to various medicaments and prescriptions which can be employed. Following a chapter of caution in which the dangers and contraindications of lavage are mentioned, the author discusses those conditions in which colonic lavage has proved beneficial, and one is impressed with the multiplicity of these conditions. Few of us would agree with the apparent intimation that there are definite irrigations for specific disturbances and that formula No. 22 is beneficial in cases of cardiac arrhythmia, prescription No. 29 in cases of arthritis with psoriasis (this prescription contains radium emanation), prescription No. 25 for acne, another for gout, and so on.

The book contains a mine of information in concise form, the illustrations are good and the printing excellent. It stresses an important and essential form of therapy whose limitations, however, must be recognized and not forgotten in a wave of enthusiasm.

S. M.

Modern Alchemy. By William Albert Noyes, University of Illinois, and W. Albert Noyes, Jr., Brown Universty. Ed. I. ix + 207 pages, 14 x 23 cm. Charles C. Thomas, Springfield, Ill., 1932. Price, $3.00.

In this treatise the authors have presented a panoramic view of some of the fundamental developments of the physical sciences. The style is fascinating and in some of the more intricate mathematical phenomena of physical chemistry the authors have substituted concise diction for mathematical formulae. This opens the volume to the general reader

in science, whose interests in the developments of physical chemistry are secondary.

The subjects discussed are: The Methods of Science, Atomic Structure, Transmutation of the Elements, Valence, Radiations on Chemical Systems, New Elements and New Uses for Old Ones, and the Elixir of Life.

The first chapter, "Methods of Science", embraces many of the fields of the biological and physical sciences. The interrelationship of the development of each is emphasized. Although the treatment of each subject is superficial, owing to the nature of the volume, much striking philosophy has been included. Thus under psychology one reads, "The function of philosophy is to integrate all branches of science and form from them a closely interrelated whole."

The chapter on the "Elixir of Life" should be found interesting by medical readers. Herein the history of the futile search by the chemist for the "Elixir of Life" is reviewed. The rise of iatrochemistry, the work of Pasteur, the major conquests in the field of bacteriology and the advance of chemotherapy are developed. The sociological and international difficulties involved in the control of communicable disease are discussed.

In the introduction the authors mention that the writing of this volume was suggested by the late Dr. E. E. Slosson. In the book the spirit of Slosson is perpetuated, lending to the volume a warmth of interest and ardor which was so characteristic of the pen of that great master in this field of literature.

J. C. K., Jr.

The History of Dermatology. By WILLIAM ALLEN PUSEY, A.M., M.D., LL.D., Professor of Dermatology Emeritus, University of Illinois; President of the American Dermatological Association and of the American Medical Association from time to time. Fabricoid Linen. 233 pages, 33 illustrations. Charles C. Thomas, Springfield, Ill. and Baltimore, Md., 1933. Price $3.00.

Any work from the pen of William A. Pusey, the Nestor of American Dermatology, must be good, and his latest *History of Dermatology* is no exception. It is a concise, absorbing story of the growth and development of dermatology from ancient times to, and including, its present status as a branch of medicine burdened with a nomenclature fearfully and wonderfully made. The history is written in a plain unassuming style, readable and understandable by lay and professional alike. The very close, intimate, and inseparable relation between dermatology and medicine is made evident in the introduction. Since skin lesions in many instances are simply reflections of a disturbance of the general economy, it is difficult to draw a hard and fast line between the specialty and general medicine.

The early chapters deal with the development and the observations of the ancients and their interpretation of the macroscopic appearance of lesions. Later the story is taken up by periods in the various countries, Germany, Austria, Great Britain, and the United States.

It is disappointing, however, to note that Henry Stelwagon's work in dermatology is dismissed with but a few words. His monumental work on the *Diseases of the Skin* is lauded, but there is no mention of his other writings.

The intimate association of dermatology and venereal diseases as practised in foreign countries is recognized in a graphic account of the life of Neisser, whose name is inseparably associated with the discovery of the gonococcus. Ricord, whose fame rests upon his urological contributions, is given credit for his epoch-making experiments by which he differentiated the local results of the inoculation of gonorrhoeal pus from the systemic reaction of pus originating from a primary luetic lesion.

A unique and praiseworthy contribution to the literature is an *Historical Index of Dermatology* in which is given historically a sketch of the various diseases from Acanthosis Nigricans to Zona.

The appearance of the volume is not to be overlooked. It is printed on heavy glazed paper in large readable type. The cover design and the binding of fabricoid linen are additional attractive features. The numerous illustrations and photographs are unusually well reproduced and of a kind seldom seen in historical works.

The volume should find a place not alone in the library of every dermatologist but should be read and treasured by everyone interested in the growth and development of medicine.

M. S. R.

GEORGE MORRIS PIERSOL, B.S., M.D., Philadelphia
President, 1933-1934

GEORGE MORRIS PIERSOL, B. S., M. D.,

Philadelphia

President of the AMERICAN COLLEGE OF PHYSICIANS

1933 - 1934

Born, Philadelphia, October 13, 1880; graduated, William Penn Charter School, 1898; University of Pennsylvania, B. S., 1902; University of Pennsylvania School of Medicine, M.D., 1905.

Resident Physician (1905-1906), and Chief Resident Physician (1906-1907), Hospital of the University of Pennsylvania, Philadelphia; Prosector to the Professor of Anatomy (1907-1910), and Associate in Medicine (1912-1921), University of Pennsylvania School of Medicine; Physician, Episcopal Hospital, Philadelphia, 1912-1916; Professor of Medicine, Woman's Medical College of Pennsylvania, 1917-1922; Lieutenant Colonel, Medical Corps, U. S. Army, 1917-1919; Commanding Officer, U. S. Army, Base Hospital No. 20, A.E.F., 1918; Medical Consultant, Fourth Army Corps, A.E.F., 1918-1919.

Professor of Medicine and Vice Dean of Medicine, Graduate School of Medicine of the University of Pennsylvania; Physician, Graduate Hospital of the University of Pennsylvania; Physician-in-Chief, Abington Memorial Hospital, Abington; Active Consultant in Medicine, Philadelphia General Hospital; Consultant to the Preston Retreat and the Chestnut Hill Hospital; Medical Director, Bell Telephone Company of Pennsylvania; Editor, *The Cyclopedia of Medicine*; ex-Editor, *The American Journal of Medical Sciences*; author of numerous medical articles.

Member: Delta Tau Delta, Alpha Mu Pi Omega, Sigma Xi and Alpha Omega Alpha fraternities; Member and ex-President, Philadelphia County Medical Society; Member, Medical Society of the State of Pennsylvania; Fellow, American Medical Association; Member, Association of American Physicians; Member and ex-President, American Gastro-Enterological Association; Member and ex-President, American Climatological and Clinical Association; Fellow, College of Physicians of Philadelphia; Member, Philadelphia Pathological Society; Member, Philadelphia Pediatric Society.

Dr. Piersol became a Fellow of the College in 1922. From 1926 to 1932 he held the office of Secretary-General. He served on the Committee on Credentials for six years and gave unstintingly of his time to this laborious task. In spite of many other activities and heavy responsibilities he has always given freely of his energy and ability to the work of the College. He enters upon his term as President with an intimate knowledge of the College's problems and with a wide acquaintanceship and popularity among its Fellows.

JONATHAN CAMPBELL MEAKINS, M.D.C.M., LL.D. (Edin.), Montreal
President-Elect, 1933-1934

JONATHAN CAMPBELL MEAKINS, M.D.C.M., LL.D. (Edin.),
F.A.C.P., F.R.C.P. (C), F.R.C.P. (EDIN.), HON. F.R.C.S. (EDIN.),
F.R.S.C., F.R.S.E.,

Montreal

President-Elect of the AMERICAN COLLEGE OF PHYSICIANS

1933 - 1934

Born, Hamilton, Ontario, May 16, 1882. Graduated, Hamilton High School; McGill University, M.D.C.M., 1904. Resident Physician, Royal Victoria Hospital, Montreal, 1904-1906; Assistant in Medicine, Johns Hopkins Hospital, 1906-1907; Resident Pathologist, Presbyterian Hospital, New York City, 1907-1909; Lecturer in Clinical Medicine, McGill University, and Assistant Physician, Royal Victoria Hospital, 1909-1913; Canadian Army Medical Corps, 1914-1918; Member, Inter-Allied Chemical Warfare Conference; Consultant Physician, Canadian Army Medical Corps, 1918-1919; Christison Professor of Therapeutics and Professor of Clinical Medicine, Edinburgh University, 1919-1924; Director of Medical Research Laboratories, Edinburgh University and Royal Infirmary, 1920-1924; Consulting Physician, Royal Maternity and Simpson Memorial Hospital, Edinburgh, 1923-1924.

Director of the Department of Medicine and Professor of Medicine, McGill University, Montreal; Director of the University Clinic, McGill University; Physician-in-Chief, Royal Victoria Hospital, Montreal.

Member: The Physiological Society (Great Britain); The British Medical Association; The Canadian Medical Association; Association of American Physicians; The American Physiological Society; Society of Experimental Biology and Medicine; The Montreal Medico-Chirurgical Society; and others.

Dr. Meakins has made numerous and important contributions to the medical literature in many fields. His investigations on the pathological physiology of the respiration and the circulation are very widely known.

Dr. Meakins was elected a Fellow and a Regent of the American College of Physicians in 1928. He was appointed Chairman of the Seventeenth Annual Clinical Session in Montreal, the first meeting of the College in Canada. Under his guidance, this very successful meeting set a high standard in the excellence of arrangements and the quality of the program of clinics.

College News Notes

Dr. Henry J. John (Fellow), Cleveland, Ohio, and Dr. William D. Sansum (Fellow), Santa Barbara, California, are members of the Advisory Editorial Board of the newly established journal, *Diabetes*, which made its first appearance in November, 1932.

Major George R. Callender (Fellow), Fort Sam Houston, Texas, has been elected President of the American Society of Tropical Medicine for the year 1933.

At a dinner given in his honor at the Drake Hotel, Chicago on January 3, 1933, the Honorable René Weiller, Consul-General of France, awarded to Dr. Frank Smithies the Cross of Knight of The Legion of Honor of The French Republic in recognition of his achievements with respect to Post-Graduate Medical Education in France and in medical science.

SOCIETY FOR THE ADVANCEMENT OF GASTROENTEROLOGY

The objects of the Society are:

(a) To unite in one organization those physicians who are engaged in the specialty of Gastroenterology.

(b) To correlate closely the clinical and experimental work of the specialty as it is performed everywhere and to make practical application of all recent advances in this field.

(c) To stimulate and encourage research work in every phase of Gastroenterology.

(d) To act as a control agency through which all qualifications and all requirements relating to the specialty may be standardized.

(e) To formulate the highest standards and principles for the practise of the specialty.

(f) To encourage legislation and public support as related to the specialty.

(g) To edit and publish the proceedings of the Society and all matters, papers, articles, subjects and reports considered.

Officers Elected for 1933

Dr. G. Randolph Manning.....President
Dr. I. L. Ritter.....1st Vice-President
Dr. E. Katz.....2nd Vice-President
Dr. Wm. C. Jacobson.....Secretary
Dr. S. Mufson.....Treasurer
Dr. S. Weiss.....Editor-in-Chief

Advisory Board

Dr. E. L. Kellogg, Honorary President
Dr. Max Einhorn
Dr. Jacob Kaufmann
Dr. Anthony Bassler
Dr. A. F. R. Andresen

Meetings are held on the fourth Wednesday of the month.

OBITUARIES

DR. WILLIAM SYDNEY THAYER

William Sydney Thayer, Fellow of the American College of Physicians, died suddenly of heart failure on December 10, 1932.

Dr. Thayer was born into a distinguished New England family at Milton, Massachusetts, on June 23, 1864. On his maternal side he was descended from Ralph Waldo Emerson; his father, James Bradley Thayer, and a brother, Ezra Thayer, held chairs in the Law School of Harvard University. Reared in the university atmosphere of Cambridge, where he lived

after the age of ten, he never lost contact with Harvard. He was graduated from the University as Bachelor of Arts in 1885, and as Doctor of Medicine in 1889, served as Visiting Physician (pro tem) at Peter Bent Brigham Hospital in 1914, and had completed two terms, beginning 1915, as a member of the Board of Overseers of Harvard University.

Meanwhile, he had been called to Baltimore by Osler from the Massachusetts General Hospital in 1890, and for the remaining forty-two years of his life he made his home in this city. He was, successively, Assistant Resident Physician, Resident Physician, and Head of the Medical Department of the Dispensary (1898-1906) of the Johns Hopkins Hospital. He practised medicine and held the position of Professor of Clinical Medicine in Johns Hopkins University from 1905 to 1918. In June 1917, he went to Russia as a member of the Red Cross Mission, and in March 1918, entered upon active duty with the United States Army in France and was appointed Chief Consultant, Medical Services, A.E.F., in June 1918; Brigadier-General, October 1, 1918. While in France he was asked to accept the position of Professor of Medicine on the university basis at Johns Hopkins. Returning from France, he relinquished his practice and held this post together with that of Physician-in-Chief of the Johns Hopkins Hospital until 1921. He then resigned, resumed his consultation practice, and became Emeritus Professor of Medicine; he continued to teach until the day of his death.

Many honors were heaped upon him. He was President of the American Society of Tropical Medicine (1910), President of the American Society for Clinical Investigation (1913), President of the Congress of American Physicians and Surgeons (1915), of the Association of American Physicians (1921), and of the American Medical Association (1928-1929). He held honorary degrees from Washington College, University of Edinburgh, University of Chicago, University of Paris, and McGill University. He held Honorary Membership in the Therapeutical Society of Moscow, in the Association of Physicians of Great Britain and Ireland, and in the Industrial Society of Medical Hydrology. He was Honorary Fellow of the Royal Society of Medicine of Budapest, of the Royal College of Physicians of Ireland, of the Royal Society of Tropical Medicine and Hygiene, London, of the Royal Society of Medicine, London, and of the Royal College of Physicians of Edinburgh. He was associate foreign member of the Académie de Médicine, Paris, corresponding member of the Société des Hôpitaux de Paris, of the Société des Hôpitaux de Lyon, and of the Société Royale des Sciences Médicales et Naturelles de Bruxelles. His other affiliations and honors, some of outstanding importance, are too numerous to record in full; mention must be made, however, of his appointment to Commander, Legion of Honour (1927), and of his selection as Orator at the Bright Centenary at Guy's Hospital in 1927.

Dr. Thayer married Miss Susan Chisolm Read, of Charleston, S. C. in 1901. Although in ill health during the latter years of her life, she lived until 1917, and died during her husband's

absence in Russia. No children survive.

The loss to the medical profession of the United States from the death of Dr. Thayer is great; this is especially true because of the peculiarly individual nature of his contribution. The unique quality of the man lay in the imponderables of character, of brilliant linguistic accomplishment, of personal charm, of intense loyalty to persons and institutions and ideals. Though sought on every hand for the wisdom of his clinical judgment, which was second to none, he will be remembered by those who knew him best as one who transcended medicine and became a great man.

(Furnished by JOHN T. KING, JR., M.D., F.A.C.P., Baltimore, Md.)

DR. HENRY DASPIT

Dr. Henry Daspit died December 19, 1932, as a result of influenza-bronchopneumonia. He had been sick but a few days and was rapidly overwhelmed by the severity of the infection.

Dr. Daspit graduated from Tulane University in 1907 and promptly obtained a position in the Louisiana State Hospital for the Insane, at Jackson, which led to his subsequent interest in neuropsychiatry, in which he specialized thereafter. On his return to New Orleans from Jackson he served in various ranks in the Department of Nervous and Mental Diseases of Tulane Medical School, obtaining in 1921 the Professorship of Neurology and, in 1926 when the chair of Psychiatry was combined with that of Neurology, he held this twofold position. In 1928 he became Dean of the Graduate School. In addition to these two positions, at the time of his death he was a senior visiting physician at Charity Hospital, superintendent of the City Hospital for Mental Diseases and City Alienist; he was consultant in Neurology for the United States Marine Hospital No. 14 and held a similar position in some four or five other hospitals. His interest was not confined solely to his specialty and to his pedagogic activities. He was a public-minded citizen and a goodly portion of his time was occupied with many sociologic and hygienic activities.

A member of an old French family, Dr. Daspit happily combined attributes of friendliness, charm and sociability, so that he had a host of friends as well as innumerable acquaintances. Clear thinking, kindly and always willing to help others, his advice and assistance were sought by many.

He was well known in Louisiana, Mississippi, Alabama, and Texas through his contact with the undergraduate students and the graduate students of the Medical School of Tulane University. His death came as a shock to the many who had been taught by him and who have always known him as a keen, physically active, and industrious teacher.

In 1927 he became a Fellow in the American College of Physicians and was interested intensely in its activities and its program. He did much to further the purposes of the organization and was enthusiastic in his belief in what could be accomplished by it.

(Furnished by J. H. MUSSER, M.D., F.A.C.P., New Orleans, La.)

DR. FENTON BENEDICT TURCK

Dr. Fenton Benedict Turck (Associate), New York City, died November 16, 1932, of angina pectoris; aged seventy-five years.

Dr. Turck received his medical degree from the Northwestern University Medical School in 1891. He did postgraduate work at the Pathological Institute of Berlin. He was House Surgeon in the Alexian Brothers Hospital, Chicago, 1891-92; Instructor in Internal Medicine at the Postgraduate Medical School, Chicago, 1893; Lecturer, Jefferson Medical College of Philadelphia, 1896; Lecturer, University of Rome, Italy, 1906; and the Founder and Director of the Laboratory, Turck Foundation, at the time of his death.

Dr. Turck was the author of 102 articles published in the United States and Europe. During the World War, he held the rank of Captain in the Medical Corps of the U. S. Army. He was a member of King's County Medical Society, the New York State Medical Association, the American Association for Advancement of Science, the Association for the Study of Internal Secretions, the Royal Geographic Society (Lisbon), Société d'Urologie de France, and a Fellow of the American Medical Association and of the New York Academy of Medicine. He had been an Associate of the American College of Physicians for many years.

DR. ALFRED HENRY

Dr. Alfred Henry (Associate), Indianapolis, Indiana, died suddenly December 12, 1932, of angina pectoris; aged fifty-seven years.

Dr. Henry graduated from the Indiana Medical College, School of Medicine of Purdue University, Indianapolis, in 1907. He did postgraduate work at the Trudeau Sanatorium and at Bellevue Hospital of New York City. From 1914 to 1920, he was Professor of Anatomy, Normal College of Gymnastic Union; from 1916 to 1921, Professor of Physiology, Indiana Dental College; and since 1912, he had occupied various teaching positions on the staff of the Indiana University School of Medicine, being Clinical Professor of Medicine at the time of his death.

In 1911, Dr. Henry aided in the organization of the Marion County Tuberculosis Association, becoming its first president and serving in that capacity until 1927, when he retired. He was prominent in state anti-tuberculosis activities and was elected President of the Indiana Tuberculosis Association in 1917. He was a director of the Indianapolis free tuberculosis clinics from 1911 to the time of his death. In 1916, he was president of the Mississippi Valley Conference for Tuberculosis Workers. He was president of the National Tuberculosis Association for the year 1931-32.

Some of Dr. Henry's additional appointments included: President of Board of Directors, Sunnyside Sanatorium, Oaklandon; Member of Staff, St. Vincent's Methodist Hospital, Robert W. Long Hospital and the James Whitcomb Riley Hospital for Children. He had been an Associate of the American College of Physicians since 1921.

DR. GAYFREE ELLISON

Dr. Gayfree Ellison, Norman, Oklahoma, died December 22, 1932. He was born in 1875 and received his A.B. degree from Bethany College, Lindsborg, Kansas. He served in the Spanish-American War with the 7th Kansas Infantry under General Fred Funston, and took part in the pursuit and capture of Aguinaldo.

He received his M.D. degree from Rush Medical College in 1903; interned, Augustina Hospital, 1903-1904; assistant to Dr. A. J. Ochsner, 1904-1906; practised at Muskegon, Michigan, 1906-1908; practised at Oklahoma City, 1908-1911; Bacteriologist, Oklahoma State Board of Health, 1911-1914; Professor of Bacteriology, Medical School of University of Oklahoma, 1914-1928; World War, medical service, 1917-1919; Professor of Epidemiology and Public Health, 1928 to time of death. He was also school physician in charge of student health in the University of Oklahoma from 1928 until the time of death.

Dr. Ellison was a member of Cleveland County Medical Society, Oklahoma City Academy of Medicine, Oklahoma State Medical Association, American Medical Association, Southern Medical Association, Society of American Bacteriologists, and a Fellow of the American College of Physicians.

Dr. Ellison left a wife, a son, Gayfree, and a daughter, Helena. He was a man of exceedingly high principles, a student, and had the highest ideals of medicine. He had always taken an active part in the betterment of the medical profession in his local, state and national affairs.

(Furnished by LEA A. RIELY, M.D., F.A.C.P., Governor for Oklahoma.)

DR. EDWARD LOUIS HEINTZ

Dr. Edward Louis Heintz (Fellow), Chicago, Ill., died suddenly December 7, 1932, of heart disease; age fifty-eight years.

Dr. Heintz was born in Rolla, Mo., April 27, 1874. He attended the University of South Dakota from 1891 to 1893, which institution honored him in 1922 with an LL.D. degree. He graduated from the St. Louis College of Pharmacy in 1898, with the degree of Ph.G., and from the University of Illinois College of Medicine, 1901, with the degree of M.D. For many years he occupied the chair of Assistant Professor of Medicine and Clinical Medicine at the University of Illinois College of Medicine, having retired to emeritus rank at the time of his death. Dr. Heintz was Attending Physician to the University Hospital, and Secretary of the University Hospital School of Nursing. He was a member of the Illinois State Medical Society, the Chicago Medical Society, the Research Club of the University of Illinois College of Medicine and a Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1919.

Dr. Heintz was also active in civic and public affairs, being Chairman of a Chamber of Commerce Committee, working toward the development of a large park around the west side schools and hospitals. He was a member, and for over thirty years a Grand Officer, of the Alpha Kappa Kappa Fraternity.

DR. FREDERICK TREMAINE BILLINGS

Dr. Frederick Tremaine Billings (Fellow), Pittsburgh, Pa., died January 5, 1933; aged fifty-nine years.

Dr. Billings was born at Ridgewood, N. J., attended Public Schools in Washington, D. C., the Lake Mohican Military Academy and the United States Naval Academy at Annapolis, Maryland. He received his medical training at Yale University, graduating in 1898. Dr. Billings interned at Patterson (N. J.) General Hospital, and in 1922 became chief examiner of the Equitable Life Assurance Society, whereupon he went to Pittsburgh.

Dr. Billings served on the staffs of several Pittsburgh Hospitals including the Allegheny General, St. Joseph's, St. Francis, Western Pennsylvania, Presbyterian and Southside Hospitals. At one time he was chief of the University of Pittsburgh Medical Dispensary and was an instructor in Internal Medicine in that institution. During the World War he held the rank of Lieutenant Commander in the Medical Corps of the U. S. Navy (Reserve Forces).

Dr. Billings was a member of the Allegheny County Medical Society, the Pennsylvania State Medical Society, the Pittsburgh Academy of Medicine, the Central States Pediatric Society and of the American Medical Association. He had been a Fellow of the American College of Physicians since 1919.

(Furnished by E. Bosworth McCready, M.D., F.A.C.P., Governor for Western Pennsylvania.)

DR. FRANK HARTON PRATTEN

Dr. Frank Harton Pratten (Fellow) London, Ontario, although suffering with hypertension for the past year, died rather unexpectedly December 10, 1932; aged forty-six.

Dr. Pratten was born in Waterford, Ontario, obtained his elementary education in Ontario and graduated in medicine from the University of Toronto in 1911. He was Resident Physician of Muskoka Hospital for Consumptives at Gravenhurst from then until 1914, when he became a member of the staff of the Toronto General Hospital, remaining there until he went overseas in 1915. He was in charge of the chest wards at Moore Barracks' Hospital for some time, following which he served with a front line unit in France, taking part in the historic engagement of Vimy Ridge. He returned to England, in 1917, as officer in charge of medicine at the Canadian Special Hospital, Diseases of the Chest, at Lenham, Kent. He attained the rank of major during his army service. Shortly after demobilization in 1919, he became Medical Superintendent of Queen Alexandria Sanatorium at Byron.

The steady growth of the Sanatorium at Byron, from 250 beds in 1919 to 600 beds at present, and the high standard of efficiency which it has maintained are monuments to the administrative ability of Dr. Pratten. Although burdened with the affairs of so large an institution, he was never too busy to receive his medical associates, students, patients or anyone to

whom he could give an encouraging word or helpful bit of advice.

Dr. Pratten, along with his administrative ability, was an outstanding authority on diseases of the chest. He had been a Fellow of the American College of Physicians since 1923. He was also a Fellow of the Royal College of Physicians of Canada, a member of the Western Ontario Academy of Medicine, the Academy of Medicine of Toronto, the Harvey Club of London, the Ontario Medical Association, the Canadian Medical Association, the Ontario Laennec Society, and for several years had been a member of the Executive Council of the Canadian Tuberculosis Association.

He was a retiring man and, although well known in the medical world to which he devoted his life and talents, he was unknown to many outside the profession. However, those who were privileged to know him sense keenly the great loss, not only to the medical world but to humanity at large, in the untimely demise of a man whose outlook on life was an inspiration to those with whom he came in contact. The funeral services were attended by many of his fellows in the Ontario Laennec Society from all parts of the Province who paid loving tribute to a beloved associate. His ashes will lie in St. Luke's-in-the-Garden, the little chapel on the Sanatorium grounds, a building dear to his heart, on the details of which he devoted much time and care; a building which he happily lived to see completed and consecrated for service.

(Furnished by JABEZ ELLIOTT, M.D., F.A.C.P., Governor for Ontario.)